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THE JOURNAL

OF

EXPERIMENTAL MEDICINE

EDITED BY

SIMON FLEXNER, M.D.

VOLUME XXIV, NO. 2 AUGUST 1, 1916

PUBLISHED MONTHLY

AT 2419-21 GREENMOUNT AVE., BALTIMORE, MD.

BY THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH

Entered as second-class matter at the Post Office at Baltimore, Md., under the Act of March 3, 1879

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WAVERLY PRESS
THE WILLIAMS & WILKINS COMPANY
BALTIMORE, U. S. A.

A CONTRIBUTION TO THE CHEMOTHERAPY OF TUBERCULOSIS.

First Experimental Report.*

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(*From the Kitasato Institute for Infectious Diseases, Tokyo, Japan.*)

Plates 11 to 15.

(Received for publication, December 1, 1915.)

I.

Since the epoch-making discovery of Ehrlich and Hata in the treatment of syphilis, various investigators have attempted to apply chemotherapy to tuberculosis. The results of my experiments, up to the present, will be given in this communication.

In 1890 Koch reported before the Tenth International Medical Congress that the influence of telepine oil, aromatic substances, β-naphthylamine, *p*-toluidine, xylidine, dyes such as fuchsine, gentian violet, methylene blue, quinoline yellow, auramin, the steam of mercury, and chemical substances containing silver or gold, had been tested upon the growth of tubercle bacilli. Of these, potassium auricyanide was found to have remarkable germicidal power. In a dilution of 1 : 2,000,000 it kills the tubercle bacillus *in vitro*, but is powerless *in vivo*. Although the cyanides of various metals have certain specific affinities for the tubercle bacillus, yet potassium auricyanide seems to change into an inert substance by the action of the organic cells even before it reaches the tubercular lesion or the bacillus itself. While I was working on experiments to prove this point, Fischer reported that the excretions of the epidermis of a tubercular patient, as well as tuberculin, may prevent 0.5 per cent solution of potassium ferrocyanide and 1 per cent solution of ferric chloride from combining to form Berlin blue. This shows that the excretions may combine with one of the two chemical substances before they combine with each other. On the other hand, Finkler, von Linden, Meissen, Strauss, and others, reported that copper exerts an influence on the tubercle bacillus, and I have also proved this by experiments.

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*The original paper in Japanese was read before the Alumni Meeting of the Kitasato Institute for Infectious Diseases, Tokyo, Apr. 4, 1915.

I prepared a compound of copper and cyanide, both of which are known to exert an influence on the tubercular lesion. This compound may have an injurious effect upon the organic body unless it is treated chemically before being introduced into the body. The chemical compound, which is the subject of this article, has been prepared with a specific treatment so as to lessen the lesional reaction. With this product I have made experiments in the chemotherapy of tuberculosis.

Preliminary Experiments.

Guinea pigs were employed in the preliminary experiments. 2 mg. of the human type of the tubercle bacillus were introduced under the skin on the left side of the chest, and observations recorded of the effect of the preparation upon the duration of life, body weight, and macroscopical changes of various organs, as well as of the microscopical changes and the number of tubercle bacilli. Of six guinea pigs injected with tubercle bacilli, three were kept as controls and the remaining three were treated with the chemical preparation.

0.5 cc. (0.1 of a lethal dose) of the solution of potassium cyanide, diluted 1 : 10,000, was given subcutaneously every other day. All the experimental animals died after gradual loss of body weight, while the controls remained comparatively healthy. The macroscopic and microscopic changes in the treated animals exceeded those of the controls. In a dilution of 1 : 1,000, however, this chemical preparation will inhibit the growth of the tubercle bacillus *in vitro*.

The potassium cyanide was treated with a specific manipulation in order to prevent the formation of free hydrogen cyanide and the subsequent chemical changes into potassium and ammonium formate, which process is accelerated by heating. The preparation thus treated has been found not to decompose even after a lapse of 6 months. The chemical substance thus prepared is called Liquid A. The lethal dose of this solution is 0.025 gm. per kilo of body weight in rabbits, and 0.005 gm. per 100 gm. of body weight in guinea pigs. In this case Control Animal 1 died of general miliary tuberculosis 11 weeks after the injection of the tubercle bacilli, preceded by loss of body weight and dyspnea. The treated animals, on the contrary,

began to increase in body weight and were livelier in their movements, and I therefore killed them 1 week after the death of the control animal. In the controls large numbers of bacilli were found in the lungs, liver, and spleen, while in Treated Animals 2 and 3, which received the hypodermic injection of the liquid, these organs contained few or even practically no bacilli. Moreover, the infection site of the treated animals consisted of an inactive cicatrix, as observed under the microscope, while that of the control was in a progressive state. In Treated Animal 4, which received the injection of the liquid at an interval of 5 weeks from the time of infection, the infection site was not healed, and the left inguinal gland showed a cheesy degeneration. Microscopical examination showed the tuberculosis still to be progressive, yet a remarkable elimination of the bacilli and an increase in body weight were also observed. From these results it may be inferred that tubercle-infected animals that receive hypodermic injections of Liquid A will outlive the control animals, and present a marked arrest of the pathological lesions. In order to determine the curative effect of Liquid A, the experiment was repeated with the results shown in Table I.

Advancing tuberculosis indicates active inflammation around the lesion where the nodules are present, dilatation of the blood vessels, and infiltration of the leukocytes and small round cells. Sometimes the nodules contain giant cells, accompanied by marked cheesy degeneration and with small production of epithelial cells.

Suspended tuberculosis indicates that the lesions contain giant cells and present cheesy degeneration, but show little inflammation about the edges of the nodules or in the surrounding tissues, while a vigorous growth of epithelial cells is taking place, accompanied by infiltration of small round cells.

Arrested tuberculosis indicates that the lesion is devoid of giant cells or cheesy degeneration, while the nodules themselves are changed into connective tissue, perhaps surrounded by muscle tissue, with only slight infiltration of small round cells.

Control Animal 5 died of general miliary tuberculosis in 12 weeks (Table II); Treated Animals 7 and 11 lived in apparent health for 10 months, when they were killed for examination. No. 6 died of cold in 21 weeks; No. 8 of a bite in 22 weeks; No. 9 of hemorrhage into the abdominal cavity in 22 weeks; No. 10 of an external wound in 27 weeks; No. 13 of ascites in 22 weeks. Microscopical examination showed that only in No. 11 were progressive pathological changes present, while the remaining seven treated animals harbored a small number of

TABLE I.

Curative Effect of Liquid A.

No. of animal.	Weight.	Duration of life.*	Change in body weight.	Macroscopic changes.	Microscopic changes.†	No. of bacilli.
			Control.			
	gm.	*wks.*	*gm.*			
1	245	11 +	−50	*Infection site:* ulceration. *Lymph glands:* swelling, cheesy degeneration. *Lungs:* cheesy pneumonia. *Liver:* m. t. *Spleen:* " "	*Lungs:* p. t. *Liver:* " " *Spleen:* " "	+++ +++ +++
			Hypodermic injection of 0.5 cc. of Liquid A every other day.			
2	275	12 ⊕	+27	*Infection site:* cicatrization. *Lymph glands:* swelling size of pea. *Lungs, liver, and spleen:* 1 or 2 nodules in each.	*Lungs:* s. t. *Liver:* " " *Spleen:* " "	− − −
3	270	12 ⊕	+180	Same as No. 2.	*Lungs:* s. t. *Liver:* " " *Spleen:* " "	− − +
4	250	12 ⊕	+200	*Infection site:* ulceration. *Lymph glands:* swelling, central cheesy degeneration. *Lungs, liver, and spleen:* 1 or 2 nodules in each.	*Lungs:* p. t. *Liver:* " " *Spleen:* " "	+ − +

*⊕, killed; +, died; +++, very many bacilli; ++, many bacilli; +, more than 10 in the whole surface of the preparation; −, negative on microscopical examination.

† p. t., progressive tuberculosis; m. t., miliary tuberculosis; s. t., suspended tuberculosis; c. t., cured tuberculosis.

TABLE II.

Experiments with Liquid A.

No. of animal.	Weight.	Duration of life.	Change in body weight.	Macroscopic changes.	Microscopic changes.	No. of bacilli.
			Control.			
	gm.	*wks.*	*gm.*			
5	550	12 +	−150	*Infection site:* ulceration, pustulation. *Lungs:* cheesy degeneration. *Liver:* m. t. *Spleen:* general cheesy degeneration.	*Lungs:* p. t. *Liver:* " " *Spleen:* " "	+++ +++ +++
			Hypodermic injection of 0.5 cc. of Liquid A every other day.			
6	450	21 +	+150	*Infection site:* ulceration. *Lymphatic glands:* swelling size of pea. *Lungs:* brown pigment infiltrated. *Liver:* 1 or 2 nodules. *Spleen:* few nodules.	*Lungs:* s. t. *Liver:* " " *Spleen:* " "	+ − +
7	450	43 ⊕	+305	*Infection site:* cured, cicatrization. *Lymphatic glands:* large as tip of small finger, central cheesy degeneration. *Lungs:* no change. *Liver:* indurated. *Spleen:* no change.	*Lungs:* s. t. *Liver:* " " *Spleen:* " "	+ − +
8	350	22 + (External wounds.)	+150	Same as No. 7, but no swelling in the lymphatic glands.	*Lungs:* s. t. *Liver:* " " *Spleen:* " "	+ + +

TABLE II—*Concluded.*

No. of animal.	Weight.	Duration of life.	Change in body weight.	Macroscopic changes.	Microscopic changes.	No. of bacilli.
	gm.	*wks.*	*gm.*			
9	450	26 +	+100	Same as No. 8.	*Lungs:* s. t. *Liver:* " " *Spleen:* " "	+ + +
10	500	39 + (Intestinal catarrh.)	+250	Same as No. 8.	*Lungs:* s. t. *Liver:* " " *Spleen:* " "	+ + +
11	450	43 ⊕	−120	*Infection site:* cured, cicatrization. *Lymphatic glands:* no swelling. *Lungs:* m. t. *Liver and spleen:* no change.	*Lungs:* p. t. *Liver:* s. t. *Spleen:* " "	++ ++ ++
12	500	26 + (External wound.)	+200	*Infection site:* cured, cicatrization. *Lymphatic glands:* no swelling. *Lungs, liver, and spleen:* 1 or 2 nodules.	*Lungs:* s. t. *Liver:* " " *Spleen:* " "	+ + +
13	450	36 +	−+	*Infection site:* cured, cicatrization. *Ascites:* about 50 cc. *Lungs:* no change. *Liver:* indurated. *Spleen:* normal size, m. t.	*Lungs:* s. t. *Liver:* " " *Spleen:* " "	+ + +

the bacilli only. In other words, the pathological changes were arrested. These results agree with those of the original experiment in which a marked improvement in the course of the tuberculosis was noted.

Experimental Ophthalmic Tuberculosis in the Rabbit.

For the purpose of determining the influence of Liquid A upon tubercular lesions, experiments with guinea pigs are inconvenient, for the animals must either be allowed to die or they must be killed before any changes can be detected. Hence I injected the human type of tubercle bacilli into the aqueous chamber of the eye of the rabbit, in which situation the changes could be observed freely.

TABLE III.

Experimental Ophthalmic Tuberculosis in Rabbits Treated with Liquid A.

No. of animal.	Weight.	Duration of life.	Change in body weight.	Macroscopic changes.	Microscopic changes.	No. of bacilli.
			Control.			
	gm.	*wks.*	*gm.*			
1	2,550	9 ⊕	−200	General ophthalmic tuberculosis. *Lungs:* metastatic m. t.	*Eyeball:* p. t. *Lungs:* " "	+++ +++
			Injection of 5 cc. of Liquid A every other day.			
2	2,100	5 + (Abortion.)	+150	*Right iris:* 4 nodules. *Lungs:* no nodules.	*Eyeball:* s. t. *Lungs:* normal.	++ −
3	2,100	7 + (Ileus.)	+250	Same as No. 2.	*Eyeball:* s. t. *Lungs:* pneumonia by foreign body.	++ −
4	1,700	9 ⊕	+200	Same as No. 2.	*Eyeball:* s. t. *Lungs:* " "	++ +
			Control.			
5	1,000	56 ⊕	+1,600	General ophthalmic tuberculosis. *Lungs:* m. t.	*Eyeball:* p. t. *Lungs:* " "	+++ +++
			Injection of 7 cc. every other day, first 2 times; 2.0 cc. every other day since then.			
6	2,000	56 ⊕	+1,250	*Iris:* cured, cicatrization. *Lungs:* normal.	*Eyeball:* c. t. *Lungs:* " "	− −

Table III indicates that Control Animal 1 developed first tubercular nodules on the surface of the iris. These gradually increased in number and volume and contained a large number of bacilli, and finally underwent cheesy degeneration leading to severe miliary tuberculosis. On the other hand, Treated Animal 2 presented five nodules at the edge of the pupil, which, however, soon disappeared. The four nodules appearing on the surface of the iris remained stationary and were confirmed by autopsy. Treated Animal 3 developed an irregular pear-shaped pupil in consequence of an adhesion of the iris and cicatrization. The tubercular nodules were surrounded by newly formed connective tissue, and a calcareous deposit took place within the cavity that had been formed by the cheesy degeneration; a few bacilli only were present. The lungs contained one or two nodules in which tubercle bacilli were not found. Treated Animal 4 presented about the same number and size of nodules present before the injection of the liquid. They contained small numbers of bacilli.

In the control animal the infection was progressive, and in the treated animals it was suspended. It therefore occurred to me that if the treatment should be continued long enough the disease might be completely healed. With this idea in mind I made another experiment with two guinea pigs. One of them, No. 5, was kept as a control. This animal developed general ophthalmic tuberculosis and miliary tuberculosis of the lung. The other, No. 6, which received continuous treatment with the liquid was completely cured, the only residue being a cicatrization at the point of inoculation. No nodules developed after a period of 6 months, and none during a succeeding period of 6 months.

Liquid A produced a congestion around the ophthalmic lesions which sometimes amounted to hemorrhage within the lesions, while the nodules became stained with the coagulated blood. Moreover, the internal pressure of the eye increased and the eyeball seemed to be pushed outwards. These phenomena disappeared with the discontinuance of the injection of the preparation and reappeared upon its renewal. On the contrary, the healthy eye seemed to be unaffected by the injection. Hence I infer that the effects are evidence of the influence of Liquid A upon the tubercular lesion. Whether the congestion and the bleeding are due to the action of the freed toxin or endotoxin of the tubercle bacilli, or whether they result from some irritant property of the liquid itself reacting on the toxin of the tubercle bacilli, has not yet been determined. It is clear, how-

ever, that the cyanide radical has a special chemical affinity for the toxin; for, as pointed out previously, the cutaneous excretion of a tubercular patient, as well as tuberculin, has an inhibiting action upon the chemical composition of Berlin blue. This fact, discovered by Fischer, is called the color reaction of the cutaneous excretion of tubercular patients. From this I conceive that congestion and bleeding of the tubercular lesions may be due to some such interaction, and the theory is supported by the fact that in a dilution of 1 : 1,000,000 to 1 : 2,000,000 potassium auricyanide will kill tubercle bacilli *in vitro*. Koch has stated that no other chemical substances produce a similar result.

First Comparative Treatment with Various Preparations.

The literature gives little information regarding the chemotherapy of tuberculosis. Schröder, Haupt, and others investigated the influence of tuberculin upon experimental ophthalmic tuberculosis, but report only negative results. Schröder referred to the fact that similar negative results have been observed by Alexander, Baumgarten, and their followers. In my experiments the disease seems to have been suspended in Treated Animals 2, 3, and 4, while in No. 6 it was completely arrested, leaving only the cicatrization after which there was no recurrence. These facts indicate that Liquid A may have a decided value in the treatment of tuberculosis.

I made a comparative study of the following three curative materials for tuberculosis, which are at present thought to be most promising. I employed two of my original preparations; that is, Liquid A and Liquid B. The latter contains one-half as much potassium cyanide as the former. The remaining three preparations are: (1) copper chloride, which has been suggested by Fischer, experimentally studied by von Linden, and clinically applied upon tubercular patients, especially in lupus, by Meissen and Strauss; (2) albumin-free tuberculin; (3) iodotuberculin. Unfortunately I could not obtain the iodotuberculin as offered by Kapsenberg, Sternberg, Bauer, and Murschhauser, and I therefore prepared a substitute by allowing 20 per cent of iodine to act upon old tuberculin (Merck). The preparation did not react to starch.

TABLE IV.

First Comparative Treatment of Tuberculosis with Various Preparations.

No. of animal.	Weight.	Duration of life.	Change in body weight.	Macroscopic changes.	Microscopic changes.	No. of bacilli.
				Controls.		
	gm.	*wks.*	*gm.*			
14	605	8 +	−125	*Infection site:* ulceration. *Lymphatic glands:* swelling size of pea. *Ascites:* about 5 cc. *Lungs:* m. t. *Liver and spleen:* general cheesy degeneration.	*Lungs:* p. t. *Liver:* " " *Spleen:* " "	+++ +++ +++
15	773	9 +	−173	*Infection site:* pustulation. *Lymphatic glands:* swelling and cheesy degeneration. *Lungs:* cheesy pneumonia. *Liver and spleen:* m. t.	*Lungs:* p. t. *Liver:* " " *Spleen:* " "	+++ +++ +++
16	552	8 + (External wounds.)	−25	*Infection site:* ulceration. *Lymphatic glands:* swelling large as tip of small finger. *Lungs and liver:* m. t. (Spleen was eaten by rats.)	*Lungs:* p. t. *Liver:* " "	+++ +++
17	580	9 +	−38	Same as No. 15.	*Lungs:* p. t. *Liver:* " " *Spleen:* " "	+++ +++ +++

TABLE IV—*Continued.*

No. of animal.	Weight.	Duration of life.	Change in body weight.	Macroscopic changes.	Microscopic changes.	No. of bacilli.
	gm.	*wks.*	*gm.*			
18	577	11 +	−119	*Infection site:* cured, cicatrization. *Lymphatic glands:* swelling size of pea. *Lungs:* cheesy pneumonia. *Liver and spleen:* general cheesy degeneration.	*Lungs:* p. t. *Liver:* " " *Spleen:* " "	+++ +++ +++
19	400	9 +	−92	*Infection site:* ulceration. *Lymph glands:* swelling and cheesy degeneration. Right pleural cavity contained about 5 cc. of serous excretion. *Lungs, liver, and spleen:* same as No. 18.	*Lungs:* p. t. *Liver:* " " *Spleen:* " "	+++ +++ +++
20	720	6 +	−94	Same as No. 14. (Ascites about 25 cc.)	*Lungs:* p. t. *Liver:* " " *Spleen:* " "	+++ +++ +++
21	660	6 +	−45	Same as No. 15.	*Lungs:* p. t. *Liver:* " " *Spleen:* " "	+++ +++ +++
22	480	11 +	−93	Same as No. 14.	*Lungs:* p. t. *Liver:* " " *Spleen:* " "	+++ +++ +++
23	570	10 +	−+	Same as No. 14.	*Lungs:* p. t. *Liver:* " " *Spleen:* " "	+++ +++ +++

TABLE IV—*Continued.*

Copper Chloride.

No. of animal.	Weight.	Duration of life.	Change in body weight.	Macroscopic changes.	Microscopic changes.	No. of bacilli.
			The same as von Linden's 6th experiment.			
	gm.	*wks.*	*gm.*			
28	575	17 ⊕	+81	*Infection site:* drainage. *Lymph glands:* swelling size of pea. *Lungs:* several nodules big as rice grains. *Liver:* m. t. *Spleen:* " "	*Lungs:* p. t. *Liver:* " " *Spleen:* " "	+++ +++ +++
29	465	13 +	−52	Not clear.	Not clear.	Not clear.
			The same as von Linden's 4th experiment.			
30	625	4 +	−90 (Mortification of site.)	*Infection site:* ulceration. *Lymph glands:* swelling, with central large cheesy degeneration.	*Lungs:* p. t. *Liver:* " " *Spleen:* " "	+++ +++ +++
			The same as von Linden's 5th experiment.			
31	500	12 +	−18	*Infection site:* cured, cicatrization. *Lymph glands:* no swelling. *Lungs:* m. t. *Liver and spleen:* both slightly swollen.	*Lungs:* s. t. *Liver:* " " *Spleen:* " "	++ + +
32	515	8 +	−4	Same as No. 31.	*Lungs:* s. t. *Liver:* p. t. *Spleen:* s. t.	+ ++ +

TABLE IV—*Continued.*

Albumin-Free Tuberculin.

No. of animal.	Weight.	Duration of life.	Change in body weight.	Macroscopic changes.	Microscopic changes.	No. of bacilli.
Doses the same as those used by Schröder.						
	gm.	*wks.*	*gm.*			
33	640	11 +	−108	*Infection site:* ulceration; flowing pustulation. *Lymph glands:* swelling size of pea. *Lungs:* cheesy pneumonia. *Liver and spleen:* cheesy degeneration.	*Lungs:* p. t. *Liver:* " " *Spleen:* " "	+++ +++ +++
34	535	4 + (Anaphylaxis.)	−55	Same as No. 33, with about 25 cc. ascites.	*Lungs:* p. t. *Liver:* " " *Spleen:* " "	+++ +++ +++
35	560	6 +	−22	Same as No. 34.	*Lungs:* p. t. *Liver:* " " *Spleen:* " "	+++ +++ +++
36	335	7 + (Hemorrhage into abdominal cavity.)	+113	*Infection site:* cured, cicatrization. *Lymph glands:* central cheesy degeneration size of pea. *Lungs:* 1 or 2 nodules. *Liver:* no change. *Spleen:* m. t.	*Lungs:* s. t. *Liver:* " " *Spleen:* " "	+ + +
37	360	10 +	+67	*Infection site:* ulceration. *Lymph glands:* swelling size of pea. *Lungs:* cheesy pneumonia. *Liver:* no change. *Spleen:* cheesy degeneration.	*Lungs:* p. t. *Liver:* s. t. *Spleen:* p. t.	+++ ++ +++

TABLE IV—*Continued.*

Iodotuberculin.

No. of animal.	Weight.	Duration of life.	Change in body weight.	Macroscopic changes.	Microscopic changes.	No. of bacilli.
Doses the same as those used by Schröder.						
	gm.	*wks.*	*gm.*			
38	540	11 + (Intestinal strangulation.)	−93	*Infection site:* ulceration; small intestine cohered to abdominal walls. *Lungs:* cheesy pneumonia. *Liver and spleen:* no nodules.	*Lungs:* p. t. *Liver:* s. t. *Spleen:* p. t.	+ + ++
39	680	7 +	−66	*Infection site:* cured, cicatrization. *Lungs:* cheesy pneumonia. *Liver:* m. t. *Spleen:* " "	*Lungs:* p. t. *Liver:* " " *Spleen:* " "	+++ +++ +++
40	480	8 +	−83	Not clear.	*Lungs:* not clear. *Liver:* " " *Spleen:* " "	+++ +++ +++
41	560	17 ⊕	+204	No marked changes.	*Lungs:* s. t. *Liver:* " " *Spleen:* " "	+ + +
42	565	17 ⊕	+107	*Infection site:* pustulation. *Lymph glands:* swelling size of pea. *Lungs:* 1 or 2 nodules. *Liver:* no nodules. *Spleen:* 1 or 2 nodules.	*Lungs:* s. t. *Liver:* " " *Spleen:* " "	+ + +

TABLE IV—*Continued.*

Liquid A.

No. of animal.	Weight.	Duration of life.	Change in body weight.	Macroscopic changes.	Microscopic changes.	No. of bacilli.
Injection of 1 cc. of Liquid A every other day.						
	gm.	*wks.*	*gm.*			
43	460	11 + (External wound.)	+72	*Infection site:* cured, cicatrization. *Lymph glands:* swelling size of pea, central cheesy degeneration. *Lungs, liver, and spleen:* no marked changes.	*Lungs:* s. t. *Liver:* " " *Spleen:* " "	+ + +
44	565	7 +	−82	*Infection site:* cured, cicatrization. *Lymph glands:* swelling size of pea. *Ascites:* about 5 cc. *Lungs:* m. t. *Liver and spleen:* 1 or 2 nodules.	*Lungs* p. t. *Liver:* s. t. *Spleen:* " "	++ + +
45	577	7 + (Bitten by a dog.)	−123	*Infection site:* cicatrization, surroundings being infiltrated. *Lymph glands:* swelling size of pea. *Lungs:* a few nodules. *Liver and spleen:* no marked changes.	*Lungs:* s. t. *Liver:* " " *Spleen:* " "	+ + +
46	538	12 +	+78	*Infection site:* cured, cicatrization. *Lymph glands:* swelling size of rice grains. *Lungs:* a few nodules. *Liver and spleen:* no marked changes.	*Lungs:* p. t. *Liver:* s. t. *Spleen:* p. t.	++ + ++

TABLE IV—*Continued.*

No. of animal.	Weight.	Duration of life.	Change in body weight.	Macroscopic changes.	Microscopic changes.	No. of bacilli.
	gm.	*wks.*	*gm.*			
47	460	7 + (Pneumonia.)	−45	*Infection site:* ulceration. *Lymph glands:* swelling size of rice grains. *Lungs:* a few nodules. *Liver and spleen:* no marked changes.	*Lungs:* p. t. *Liver:* s. t. *Spleen:* p. t.	++ + +
48	540	12 + (Ascites.)	+92	*Infection site:* cured, cicatrization. *Lymph glands:* swelling size of rice grains. *Ascites:* about 20 cc. *Lungs:* pigment infiltration. *Liver and spleen:* no marked changes.	*Lungs:* s. t. *Liver:* " " *Spleen:* " "	+ + +
49	460	12 +	+68	*Infection site:* cured by cicatrization. *Lymph glands:* swelling size of pea. *Lungs:* a few nodules. *Liver and spleen:* no marked changes.	*Lungs:* s. t. *Liver:* " " *Spleen:* " "	+ + +
50	650	9 + (Pleurisy.)	−62	*Infection site:* ulceration. *Lungs:* cheesy pneumonia. *Liver:* m. t. *Spleen:* " "	*Lungs:* p. t. *Liver:* " " *Spleen:* " "	+++ +++ +++
51	460	13 + (External wound.)	+50	No marked changes except about 10 cc. of pleural excretion.	*Lungs:* s. t. *Liver:* " " *Spleen:* " "	+ + +
52	430	17 ⊕	+176	No marked changes.	Same as No. 51.	+ + +

TABLE IV—*Concluded.*

Liquid B.

No. of animal.	Weight.	Duration of life.	Change in body weight.	Macroscopic changes.	Microscopic changes.	No. of bacilli.
Hypodermic injection of 2 cc. of Liquid B every other day.						
	gm.	*wks.*	*gm.*			
53	490	9 +	+27	*Infection site:* cured, cicatrization. *Lymph glands:* swelling size of rice grains. *Lungs:* m. t. *Liver and spleen:* no marked changes.	*Lungs:* p. t. *Liver:* " " *Spleen:* " "	++ ++ ++
54	680	13 + (Pneumonia.)	+35	Same as No. 53.	*Lungs:* p. t. *Liver:* " " *Spleen:* " "	++ +++ +++
55	618	13 +	+117	*Infection site:* cured, cicatrization. *Lungs, liver, and spleen:* a few nodules.	*Lungs:* s. t. *Liver:* " " *Spleen:* " "	+ + +
56	640	12 +	−+	Same as No. 55.	*Lungs:* s. t. *Liver:* " " *Spleen:* " "	+ + +
57	498	16 + (Pneumonia.)	+77	Same as No. 53	*Lungs:* p. t. *Liver:* " " *Spleen:* " "	++ +++ +++

Controls.

From Table IV it will be seen that Control Animals 14 and 16, 15, 17, and 19, 20 and 21, 18 and 22, and 23 died of general miliary tuberculosis in the 8th, 9th, 6th, 11th, and 10th weeks after inoculation, respectively. Microscopical examination showed progressive tuberculosis and many bacilli in all.

The time in which death occurs in experimental tuberculosis, as reported by various authors, differs according to the site of injection, the number of bacilli, and the toxicity of different strains of bacilli. Spengler reports death in 11 weeks; Schröder in from 18 to 75 days; von Linden in from 8 to 11 weeks; and Haupt in from 7 to 3 months and from 5 to 7 months, respectively. Haupt injected from 1 : 10,000 to 1 : 100,000 mg. of bacilli into the femoral muscle. The strain which I used seems to have been of medium grade of toxicity. Of the five animals treated with copper chloride, No. 28 gained in body weight and showed no objective changes in appearance until the end of the 17th week, when it was killed for examination. The macroscopic changes were conspicuous and the microscopic ones were progressive, and associated with the presence of many bacilli. No. 29 was missing. No. 30 was dead in 4 weeks; it presented extensive necrosis at the site of injection of the bacilli, and contained a great many bacilli. Nos. 31 and 32 died at the end of 12 and 8 weeks, respectively, and showed only slight macroscopic changes and small numbers of bacilli. Microscopic examination of both showed them to be in the suspended stage. Thus my tests agree with those of von Linden in bringing about improvement in experimental tuberculosis by the use of copper chloride.

Albumin-Free Tuberculin.

The albumin-free tuberculin was applied from the 4th week of inoculation in five animals. No. 34 died of anaphylactic shock. No. 37 died in 10 weeks of miliary tuberculosis, and microscopical examination showed it to be in the progressive stage. No. 33 died in 11 weeks, and microscopic examination showed numerous bacilli and progressive tuberculosis. No. 35 died in 6 weeks, and in appearance resembled No. 34. No. 36 gained in body weight and showed only slight macroscopic changes and a small number of bacilli. Microscopic examination indicated that the animal was in the suspended stage at the time that death occurred, in the 7th week, from hemorrhage into the abdominal cavity. Thus the results coincide with the view of Koch, Virchow, and Ziegler, who held that tuberculin and its derivatives tend to increase the resistance of the individual against tuberculosis and thus to improve the general condition, although without action directly on the bacilli.

Iodotuberculin.

Iodotuberculin was given hypodermically from the 4th week of infection. Animal 38 died of intestinal strangulation in consequence of cicatrization which occurred after the intestinal lesion had been cured. Small numbers of the bacilli were found in the lesion. The liver seemed to be in the suspended stage, but the lungs and the spleen appeared to be uninfluenced. No. 39 died in the 7th week. It had lost body weight, and on microscopic examination was found to be in the progressive stage with a great many bacilli. No. 40 had been kept for 8

weeks when it was lost. No. 41 gained in body weight and was killed for examination in the 17th week. It presented no conspicuous macroscopic changes, and microscopic examination showed it to be in the suspended stage, with a few bacilli only. No. 42 gained gradually in body weight. It was killed in the 17th week and showed slight macroscopic changes with few bacilli, and under the microscope proved to be in the suspended stage. Thus the iodotuberculin which I prepared yielded good results, although it may not have been identical with that prepared by Kapsenberg, Sternberg, Bauer, and Murschhauser.

Liquid A.

Liquid A was given from the 4th week after inoculation. Animal 43 gained in weight until it died from an external wound in the 11th week. It showed slight macroscopic changes with few bacilli, and microscopically was found to be in the suspended stage. No. 44 died in 7 weeks. It had progressive lesions in the lungs, but suspended ones in the liver and spleen with few bacilli. No. 45 was killed accidentally in the 7th week. It was in the suspended stage with few bacilli and showed slight macroscopic changes. Nos. 46 and 47 died in the 12th and 7th weeks, respectively. In both the liver was in the suspended stage with few bacilli, and the lungs and spleen were in the progressive stage with many bacilli. Nos. 48 and 49 both died in 12 weeks. They had both gained in body weight, had slight macroscopic changes, and microscopically were found to be in the suspended stage with few bacilli. No. 50 died of pleurisy in 9 weeks. It showed conspicuous macroscopic changes with many bacilli and was in the progressive stage. No. 51 died from an external wound. No. 52 gained in body weight and appeared healthy until it was killed for examination in 17 weeks. Macroscopically it was found to have slight changes, and microscopically was in the suspended stage.

Liquid B.

Liquid B was given to five animals. Nos. 53, 54, and 57 died in 9, 13, and 16 weeks, respectively. They showed conspicuous macroscopic changes, and were in the progressive stage with many bacilli. Nos. 55 and 56 died in 13 and 12 weeks, respectively. They both showed slight macroscopic changes and were in the suspended stage with few bacilli.

The results of the comparative study of the various preparations show that copper chloride and albumin-free tuberculin each brought about complete suspension in 1, and half suspension in 1 of the 5 experimental animals; iodotuberculin brought about full suspension in 2, and half suspension in 1 of the 5 animals; while Liquid A brought about complete suspension in 6, and half suspension in 3 of 10 animals, and Liquid B full suspension in 2 of the 5. Therefore, judged

according to efficiency, these preparations stand in the following order: copper chloride and albumin-free tuberculin are least efficient; Liquid B and iodotuberculin are more efficient; Liquid A is the most efficient. Yet Liquid A did not completely heal the tubercular lesions.

Second Comparative Treatment with Various Preparations.

Proceeding from the fact that Liquid A was more efficient than Liquid B, I prepared another solution which contained more potassium cyanide than the previous preparation, in the hope of obtaining a more efficient substance. The 1:1,000 aqueous solution of this substance was called Liquid C. Again, I prepared a double salt of copper and potassium cyanide. The aqueous solution diluted 1:2,000 was prepared and treated in the same manner as Liquid A, and called Liquid D. The lethal dose of this Liquid D is 0.001 gm. per 100 gm. of body weight for the guinea pig, and for the mouse 1 : 200,000, or more accurately 1:10,000 of the body weight. Hence an aqueous solution (1:2,000) of the original solution was prepared, and 1 cc. per kilo of body weight was injected hypodermically into guinea pigs in which experimental tuberculosis had been induced. Some of the treated animals died sooner than the controls and presented severer lesions both macroscopically and microscopically; in others the reverse was the case. The comparative study of Liquids C and D is shown in Table V.

Controls.

Control Animals 58, 59, and 60 gradually lost weight and died in 5 to 8 weeks. They showed marked macroscopic changes, and under the microscope were found to be in the progressive stage with large numbers of bacilli; Nos. 74 and 75 lived until they were killed for examination in the 22nd week. They showed no marked macroscopic changes. Under the microscope in No. 74 the lung was found to be in the progressive stage; the liver and spleen were in the suspended stage with only a few tubercle bacilli. No. 75 was also in the progressive stage, and showed a few or moderate number of bacilli.

The difference in the results may be due to the fact that when dilutions of 1 : 10,000 or 1 : 100,000 mg. of tubercle bacilli were given under the skin of the right femoral muscle of guinea pigs, as Haupt

TABLE V.

Second Comparative Treatment of Tuberculosis with Various Preparations.

No. of animal.	Weight.	Duration of life.	Change in body weight.	Macroscopic changes.	Microscopic changes.	No. of bacilli.
			Controls.			
	gm.	*wks.*	*gm.*			
58	647	6 +	−90	*Infection site:* infiltration. *Lymph glands:* swelling size of pea. *Ascites:* about 20cc. *Lungs:* cheesy pneumonia. *Liver and spleen:* no marked changes.	*Lungs:* p. t. *Liver:* " " *Spleen:* " "	+++ +++ +++
59	587	8 +	−97	*Infection site:* pustulation. *Lymph glands:* swelling size of pea; thickening, cheesy degeneration. *Lungs:* cheesy pneumonia. *Liver, spleen:* cheesy degeneration.	*Lungs:* p. t. *Liver:* " " *Spleen:* " "	+++ +++ +++
60	450	5 +	−14	Same as No. 59.	*Lungs:* p. t. *Liver:* " " *Spleen:* " "	+++ +++ +++
74	667	22 ⊕	Not clear because of pregnancy.	*Infection site:* drained pustulation. *Lymph glands:* swelling size of rice grains. *Lungs:* pigment infiltration; a few nodules. *Liver, spleen:* m. t.	*Lungs:* p. t. *Liver:* s. t. *Spleen:* " "	+ + +
75	705	22 ⊕	Same as No. 74.	Same as No. 74.	*Lungs:* p. t. *Liver:* " " *Spleen:* " "	++ ++ +

TABLE V—*Continued.*

Liquid C.

No. of animal.	Weight.	Duration of life.	Change in body weight.	Macroscopic changes.	Microscopic changes.	No. of bacilli.
Hypodermic injection of 1 cc. of Liquid C every 3 weeks.						
	gm.	*wks.*	*gm.*			
61	630	22 ⊕	+70	*Infection site:* cured, cicatrization. *Lymph glands:* swelling size of rice grains. *Lungs:* a few nodules. *Liver and spleen:* no marked changes.	*Lungs:* s. t. *Liver:* " " *Spleen:* " "	+ + −
62	690	22 ⊕	+110	Same as No. 61 except a few nodules in liver and spleen.	*Lungs:* s. t. *Liver:* " " *Spleen:* " "	+ + −
63	620	22 +	+90	Same as No. 62.	*Lungs:* s. t. *Liver:* " " *Spleen:* " "	+ + −
76	622	22 ⊕	Not clear because of pregnancy.	Same as No. 62.	*Lungs:* s. t. *Liver:* " " *Spleen:* " "	+ + −
77	755	13 +	Same as No. 76.	Same as No. 62.	*Lungs:* s. t. *Liver:* " " *Spleen:* " "	+ + −
Liquid D.						
Hypodermic injection of 1.5 cc. of Liquid D every 5 weeks.						
64	709	21 +	+61	*Infection site:* cured, cicatrization. *Ascites:* about 20 cc. *Lungs:* pigment infiltration, and 1 or 2 nodules. *Liver:* m. t. *Spleen:* " "	*Lungs:* p. t. *Liver:* " " *Spleen:* " "	++ ++ +
65	625	22 +	+110	Same as No. 64.	*Lungs:* p. t. *Liver:* " " *Spleen:* " "	+++ ++ ++

TABLE V—*Continued.*

No. of animal.	Weight.	Duration of life.	Change in body weight.	Macroscopic changes.	Microscopic changes.	No. of bacilli.
Hypodermic injection of 1 cc. of Liquid D every 5 weeks.						
	gm.	*wks.*	*gm.*			
66	612	22 ⊕	+216	No marked changes.	*Lungs:* c. t. *Liver:* " " *Spleen:* " "	− − −
67	597	29 + (Intestinal catarrh.)	+173	No marked changes.	*Lungs:* c. t. *Liver:* " " *Spleen:* " "	+ + −
68	467	5 + (Intestinal catarrh.)	+−	*Infection site:* ulceration. *Lungs:* 1 or 2 pigment infiltrations. *Liver and spleen:* 1 or 2 nodules.	*Lungs:* s. t. *Liver:* " " *Spleen:* " "	− + ++
78	727	22 ⊕	Not clear because of pregnancy.	Same as No. 68.	*Lungs:* s. t. *Liver:* " " *Spleen:* " "	+ + −
79	520	15 +	Same as No. 78.	No marked changes.	*Lungs:* c. t. *Liver:* " " *Spleen:* " "	+ + −
80	595	15 + (Inflammation of subcutaneous fat tissue.)	Same as No. 78.	Same as No. 68.	*Lungs:* s. t. *Liver:* " " *Spleen:* " "	+ + −
81	410	22 ⊕	Same as No. 78.	No marked changes.	*Lungs:* c. t. *Liver:* " " *Spleen:* " "	+ − −

TABLE V—*Concluded.*

No. of animal.	Weight.	Duration of life.	Change in body weight.	Macroscopic changes.	Microscopic changes.	No. of bacilli.
Hypodermic injection of 0.5 cc. of Liquid D every 3 weeks.						
	gm.	*wks.*	*gm.*			
69	510	19 +	+175	*Infection site:* cured, cicatrization. *Lymph glands:* big as tip of small finger. *Lungs:* 1 or 2 nodules. *Liver:* no nodules. *Spleen:* 1 or 2 nodules.	*Lungs:* s. t. *Liver:* " " *Spleen:* " "	+ − −
70	532	18 + (Inflammation of the subcutaneous fat tissue.)	+54	No marked changes.	*Lungs:* s. t. *Liver:* " " *Spleen:* " "	+ + +
71	490	20 +	+100	No marked changes.	*Lungs:* s. t. *Liver:* " " *Spleen:* " "	+ + +
Hypodermic injection of 0.25 cc. of Liquid D every 3 weeks.						
72	547	13 + (Intestinal catarrh.)	+178	No marked changes.	*Lungs:* s. t. *Liver:* " " *Spleen:* " "	+ + +
73	416	16 +	+169	Same as No. 69.	*Lungs:* s. t. *Liver:* " " *Spleen:* " "	+ − −

also reports, the animals died in from 7 to 3 and from 5 to 7 months, and therefore the date of the death of the experimental animals varied according to the site of the infection and the number and toxicity of the strain of the bacilli in question. Hypodermic injection of the bacilli does not always kill guinea pigs. Again, the duration of life as well as the microscopic findings varies according to the resistance that each animal displays towards the injection. Therefore, any representative result can be attained only by as many experiments as will yield a correct statistical approximation. In my two recent experiments, unfortunately, the guinea pigs died too soon of miliary tuberculosis to agree with the prognosis in human cases. I therefore introduced the bacilli into the veins of the treated animals. The bacillary strain was obtained through the courtesy of Dr. Shiga, and had been proven to have strong toxicity. 0.05 mg. of the strain was given intravenously. In my previous experiment subcutaneous injection of the bacilli was employed. The results, therefore, seem to be relative and not decisive.

Liquid C.

Of the five animals that had been treated with Liquid C, Nos. 63 and 77 died in 22 and 13 weeks, respectively. The remaining three animals, Nos. 61, 62, and 76, appeared healthy until the 22nd week, when they were killed for examination. They showed slight macroscopic changes with very few bacilli, and under the microscope were found to be in the suspended stage.

Liquid D.

Animals 64 and 65 received hypodermic injections of 1.5 cc. of Liquid D once every 5 weeks. The former died in 21 weeks, the latter in 22 weeks. They had both gained in body weight, but showed severe macroscopic changes, and were in the progressive stage with a great number or moderate number of bacilli. Both were worse than the controls.

Of the seven animals that have been treated with 1 cc. of Liquid D, Animals 67 and 68 died in 29 and 5 weeks of intestinal catarrh, and Nos. 79 and 80 in 15 weeks of inflammation of the subcutaneous fat tissue. Nos. 66, 78, and 81 appeared healthy until 22 weeks, when they were killed for examination. Nos. 66, 67, 79, and 81 showed no macroscopic changes, while all the others showed slight microscopic changes. Nos. 66, 67, 79, and 81 were found to be cured of tuberculosis; the rest were in the suspended stage. No. 66 was free from bacilli, and the remaining six animals were found to have few or no bacilli in their organs.

Three animals received 0.5 cc. of Liquid D once every 3 weeks. No. 69 died

in 19 weeks, No. 70 died of inflammation of the subcutaneous fat tissue in 18 weeks, and No. 71 died in 20 weeks. They had all increased in body weight and showed slight macroscopic changes and suspended lesions with only a few bacilli.

Nos. 72 and 73 received 0.25 cc. of Liquid D once every 3 weeks. The former died of intestinal catarrh in 13 weeks, and the latter died in 16 weeks. They had both gained in body weight, and similar macroscopic as well as microscopic changes occurred, as noted in the preceding animals which had received 0.5 cc. of Liquid D once every 3 weeks. From these data it may be concluded that the animals which had been treated with 1 cc. of Liquid D given once every 5 weeks showed most improvement; Liquid C is less effective. Less improvement was obtained in proportion as less of Liquid D was administered. It is especially notable that the changes in the animals which received 1.5 cc. of Liquid D were more severe than in the control animals and showed more bacilli than the latter.

To sum up the results obtained in my preliminary experiments, it may be stated that subcutaneous injection of 1 cc. of Liquid D once every 5 weeks produced prolongation of life, increase of body weight, improvement in the macroscopic changes, and a cure, as indicated by the microscopic examination. Other preparations produced some improvement in the tubercular lesions, but they were efficacious only in suspending the changes determined by microscopic examination. The dose and the best manner of administering the remedy can only be determined by further study.

The preliminary experiments described above were conducted in the Surgical Institute of the Kyoto Imperial University, in the service of Professor Ito. I desire here to express my thanks to him and to Assistant Professor Osaki for their kindness in affording me the means and direction that were necessary for carrying on my experiments.

II.

Since February, 1914, I have conducted experiments with Liquid D in experimental tuberculosis at the Kitasato Institute. I undertook to explain the inconstant effects observed; namely, that while pathological processes are made to subside in some, other animals remain indifferent to the action of the preparation. By the aid of the microscope I observed the fact that copper potassium cyanide consists of three different forms of crystals, and I have, by employing a special method, succeeded in separating the different forms. I experimented with each of the three substances and ascertained that only

one of them is effective against tuberculosis, while the remaining two have an injurious effect upon the pathological processes. Since that time I have employed only the effective substance. I have tried to see what effect this substance will have on the healthy animal.

First Animal Experiments.

Two guinea pigs were chosen for the purpose; one received five injections intravenously of 1 cc. of Liquid D per kilo of body weight once every other week, while the other received the same dose at the same interval, but subcutaneously. Both gained in body weight and showed no changes.

Liquid D will inhibit the growth of all tubercle bacilli in the common glycerin broth culture, when it is mixed in the proportion of 1 : 10,000; a solution of 1 : 15,000 will inhibit the growth of the bacilli in a blood serum agar culture. Strains fast to the drug could not be obtained, though the attempt was made during a period of 5 months.

In the following experiments I employed the human type of a certain virulent strain given me by Dr. Shiga. An emulsion was prepared and 0.05 mg. of the bacilli introduced into the femoral vein. The injection of Liquid D was begun on the 4th day after inoculation. The results of the experiment are shown in Table VI.

Controls.

From Table VI it will be seen that all five control animals died in from 4 to 14 weeks. They showed marked macroscopic changes, and were in the progressive stage of tuberculosis, as seen under the microscope, with many tubercle bacilli.

Iodotuberculin.

Five animals were treated with iodotuberculin, of which two died, one in 3, the other in 4 weeks, before the efficiency of the preparation could be seen. No. 88 died in 12 weeks. It had slight macroscopic changes and was in the suspended stage with only a few bacilli. No. 90 died in 17 weeks. It showed slight macroscopic changes, and the lung was in the progressive stage; the liver and spleen were in the suspended stage. Many bacilli were found in the lungs, but few in the liver and spleen. No. 91 died in 18 weeks. It had slight macroscopic changes; microscopically the lung was found to be in the progressive stage with few bacilli.

TABLE VI.

First Animal Experiments.

No. of animal.	Weight.	Duration of life.	Change in body weight.	Macroscopic changes.	Microscopic changes.	No. of bacilli.
			Controls.			
	gm.	*wks.*	*gm.*			
82	330	4 +	−30	Highly emaciated. *Lymph glands:* swollen and cheesy degeneration. *Lungs:* cheesy pneumonia. *Liver:* 1 or 2 nodules. *Spleen:* cheesy degeneration.	*Lungs:* p. t. *Liver:* " " *Spleen:* " "	+++ +++ +++
83	240	14 +	+20	Same as No. 82.	*Lungs:* p. t. *Liver:* " " *Spleen:* " "	++ ++ ++
84	280	9 +	−+	Same as No. 82.	*Lungs:* p. t. *Liver:* " " *Spleen:* " "	+++ +++ +++
85	355	8 +	−10	Same as No. 82.	*Lungs:* p. t. *Liver:* " " *Spleen:* " "	++ ++ +++
86	165	4 +	+30	Same as No. 82.	*Lungs:* p. t. *Liver:* " " *Spleen:* " "	+++ +++ +++
				Iodotuberculin.		
				Doses the same as those used by Schröder.		
87	340	3 +	−50	*Lymph glands:* swollen and cheesy degeneration. *Lungs:* cheesy pneumonia. *Liver:* m. t. *Spleen:* " "	*Lungs:* p. t. *Liver:* " " *Spleen:* " "	+++ +++ +++

TABLE VI—*Continued.*

No. of animal.	Weight.	Duration of life.	Change in body weight.	Macroscopic changes.	Microscopic changes.	No. of bacilli.
	gm.	*wks.*	*gm.*			
88	260	12 +	+30	No marked changes.	*Lungs:* s. t. *Liver:* " " *Spleen:* " "	+ + +
89	240	4 +	−20	*Lymph glands:* swelling size of pea. *Lungs:* m. t. *Liver:* " " *Spleen:* " "	*Lungs:* p. t. *Liver:* " " *Spleen:* " "	+++ +++ +++
90	460	17 +	+10	*Lymph glands:* swelling size of rice grains. *Lungs:* 1 or 2 nodules. *Liver and spleen:* no marked changes.	*Lungs:* p. t. *Liver:* s. t. *Spleen:* " "	++ + +
91	210	18 +	+160	Same as No. 90.	*Lungs:* p. t. *Liver:* s. t. *Spleen:* " "	+ + +

Liquid D.

Intravenous injection of 1 cc. of Liquid D every 3 weeks.

92	290	23 ⊕	+120	*Lymph glands:* big as tip of small finger. *Lungs:* 1 or 2 nodules. *Liver:* 1 " 2 " *Spleen:* 2 or 3 grayish white protuberant nodules.	*Lungs:* s. t. *Liver:* " " *Spleen:* " "	+ − +
93	400	23 ⊕	+40	*Lymph glands:* swelling size of pea. *Lungs:* 3 vacuoles and 1 or 2 nodules. *Liver:* 1 or 2 nodules. *Spleen:* 1 " 2 "	*Lungs:* s. t. *Liver:* " " *Spleen:* " "	+ + +
94	240	18 +	−30	Same as No. 92.	*Lungs:* s. t. *Liver:* " " *Spleen:* " "	+ − +

TABLE VI—*Continued.*

No. of animal.	Weight.	Duration of life.	Change in body weight.	Macroscopic changes.	Microscopic changes.	No. of bacilli.
			Intravenous injection of 1 cc. of Liquid D every other week.			
	gm.	*wks.*	*gm.*			
95	240	23 ⊕	+400	No marked changes.	*Lungs:* c. t. *Liver:* " " *Spleen:* " "	− − −
96	280	23 ⊕	+250	No marked changes.	*Lungs:* s. t. *Liver:* " " *Spleen:* " "	− 4 2
97	310	23 ⊕	+20	*Lymph glands:* swelling size of pea. *Lungs:* no marked changes. *Liver:* 1 or 2 nodules. *Spleen:* 1 " 2 "	*Lungs:* c. t. *Liver:* s. t. *Spleen:* " "	− + +
			Intravenous injection of 1 cc. of Liquid D every week.			
98	240	23 ⊕	+170	*Lymph glands:* swelling size of pea. *Lungs:* 1 or 2 nodules. *Liver and spleen:* 1 or 2 nodules.	*Lungs:* s. t. *Liver:* " " *Spleen:* " "	+ + +
99	260	9 +	+150	No marked changes.	*Lungs:* s. t. *Liver:* " " *Spleen:* " "	+ + +
100	240	15 +	+70	Not clear.	Not clear.	Not clear.
101	350	14 +	+10	Not clear.	Not clear.	Not clear.
102	280	13 +	+10	Not clear.	Not clear.	Not clear.

TABLE VI—*Concluded.*

No. of animal.	Weight.	Duration of life.	Change in body weight.	Macroscopic changes.	Microscopic changes.	No. of bacilli.
Hypodermic injection of 1 cc. of Liquid D every week.						
	gm.	*wks.*	*gm.*			
103	450	12 +	0	*Lymph glands:* swelling size of rice grains. *Lungs:* 1 or 2 nodules. *Liver and spleen:* 1 or 2 nodules.	*Lungs:* s. t. *Liver:* " " *Spleen:* " "	+ + +
104	520	13 +	−80	Same as No. 103.	*Lungs:* s. t. *Liver:* " " *Spleen:* " "	+ + +
105	375	11 +	+150	*Lymph glands:* swollen, cheesy degeneration. *Lungs:* m. t. *Lungs and spleen:* m. t.	*Lungs:* p. t. *Liver:* " " *Spleen:* " "	++ ++ +++
106	340	23 ⊕	+350	No marked changes.	*Lungs:* c. t. *Liver:* " " *Spleen:* " "	− − −
107	420	8 +	−80	*Lymph glands:* swollen. *Lungs:* m. t. *Liver:* " " *Spleen:* " "	*Lungs:* p. t. *Liver:* " " *Spleen:* " "	+++ +++ +++

Liquid D.

Three animals were treated with an intravenous injection of 1 cc. of Liquid D once every 3 weeks. No. 94 died in 18 weeks, and Nos. 92 and 93 were killed in the 23rd week. Macroscopically they showed slight changes, while microscopically they were in the suspended stage of tuberculosis. Only a few bacilli were discovered in some organs.

Of the three animals that received intravenously 1 cc. once every other week, Nos. 95 and 96 had been healthy until they were killed for examination in the 23rd week. They bore no observable macroscopic changes and showed traces of healed tuberculosis under the microscope. The former showed no bacilli, while the latter showed four in the liver and two in the spleen. No. 97 was killed in the 23rd week. It also showed slight macroscopic changes. Under the microscope

the lungs showed traces of healed tuberculosis, without any bacilli, while the liver and spleen showed suspended tuberculosis with few bacilli.

Of the five animals that received intravenously 1 cc. of Liquid D weekly, No. 98 was healthy until it was killed for examination in the 23rd week, while No. 99 died in the 9th week. Macroscopically the former had slight changes and the latter practically none. Microscopically both were in the suspended stage with few bacilli. Nos. 100, 101, and 102 died in the 15th, 14th, and 13th weeks, respectively. Unfortunately they were either badly preserved or overlooked before a thorough examination was made.

Of the five animals that received weekly hypodermically 1 cc. of Liquid D, Nos. 103 and 104 died in the 12th and 13th weeks, respectively. They both showed slight macroscopic changes, and microscopically were in the suspended stage with only few bacilli. No. 106 had been healthy until it was killed for examination in the 23rd week. It exhibited scarcely any macroscopic changes, and under the microscope showed traces of healed tuberculosis with no bacilli. Nos. 105 and 107 died in the 11th and 8th weeks, respectively. They showed remarkable macroscopic changes, and under the microscope were found to be in the progressive stage with numerous bacilli.

The first animal experiment proved that the intravenous injection of 1 cc. of Liquid D per kilo of body weight every other week gave the most satisfactory results, while the intravenous injection of 1 cc. once every 3 weeks, and either intravenous or hypodermic application of the same amount weekly, are inferior to the former. From these results I conclude that the best therapeutic dose is 0.05 of the lethal dose.

These experiments emphasized the fact that the grayish white nodules that seem to be miliary tuberculosis are merely connective tissue that has been made to protrude in consequence of the contraction of the fibrous tissue, and also that bacilli are sometimes present even in the surrounding region of the cheesy degeneration and in the giant cells.

Second Animal Experiments.

0.05 mg. of the human type of tubercle bacilli was emulsified and introduced intravenously into guinea pigs, which were kept for 25 days in the laboratory without previous treatment. At the expiration of this time they were given an intravenous injection of 1 cc. of Liquid C per kilo of body weight every other week. The whole

number of the experimental animals thus obtained was forty-six, eight of which were kept as controls.[1]

Controls.

From Table VII it will be seen that the eight control animals died in the 5th to the 16th weeks. They exhibited remarkable macroscopic changes, and under the microscope were seen to be in the progressive stage. No. 114 showed few bacilli, but the remaining seven had many.

Liquid D.

Treated Animals 116, 117, 118, 119, 120, 121, 122, 123, 124, and 125 had gained in body weight. Nos. 126, 127, 128 129, 130, 131, 132, 133, 134, and 135 had gained in weight and appeared healthy until killed for examination in the 22nd week. Nos. 127, 130, 131, and 132 showed no noteworthy changes, while Nos. 126, 128, 129, 133, and 135 showed a few grayish white nodules. On microscopic examination Nos. 127, 129, 130, 131, 132, and 133 showed traces of healed tuberculosis, while Nos. 126, 128, 134, and 135 had suspended lesions. One or two bacilli were sometimes found in the whole surface of the slide, but as a rule no bacilli were present. No. 128, which was killed on the 3rd day after an injection of Liquid D, showed only one bacillus in the lung preparation; all the pathological lesions exhibited the beginning of a remarkably active reaction. Nos. 136, 137, 138, 139, 140, 141, 142, 143, 144, and 145 died in the 11th to the 17th week; some gained in weight while others lost. On macroscopic examination Nos. 137, 138, 139, 140, and 141 exhibited no remarkable changes; Nos. 136, 142, 143, 144, and 145 showed only slight changes. On microscopic examination Nos. 137, 139, 140, and 141 showed healed tubercular lesions; Nos. 136, 138, 142, 143, 144, and 145 showed suspended ones. The liver of No. 145 showed small numbers of bacilli. Of the remaining animals, however, some harbored only one and at most seven bacilli per slide. Nos. 146 and 149 died in 11 and 14 weeks, respectively. On macroscopic examination only slight changes were visible, while microscopically the animals were found to be in the suspended stage with sometimes few and sometimes a larger number of bacilli. Animals 147, 148, 150, and 151 died in the 8th to the 16th weeks. Marked macro-

[1] This experiment was carried on during the time in which Dr. Kitasato left the Imperial Institute for the Study of Infectious Diseases and established the Kitasato Institute for Infectious Diseases. Owing to the lack of a proper animal house, the same care could not be taken of the animals, and hence they suffered somewhat from lack of regular food, and some developed diarrhea in consequence of the cold. The percentage of duration of life in this second experiment cannot therefore be established exactly.

TABLE VII.

Second Animal Experiments.

No. of animal.	Weight.	Duration of life.	Change in body weight.	Macroscopic changes.	Microscopic changes.	No. of bacilli.
			Controls.			
	gm.	*wks.*	*gm.*			
108	300	13 +	0	*Lymph glands:* swollen, cheesy degeneration. *Lungs:* cheesy pneumonia. *Liver and spleen:* cheesy pneumonia.	*Lungs:* p. t. *Liver:* " " *Spleen:* " "	+++ +++ ++
109	300	16 +	−20	*Lymph glands:* swelling size of pea. *Lungs:* cheesy pneumonia. *Liver:* no marked changes. *Spleen:* cheesy degeneration.	*Lungs:* p. t. *Liver:* " " *Spleen:* " "	++ +++ +
110	330	11 +	−20	*Lungs:* 1 or 2 nodules. *Liver:* m. t. *Spleen:* " "	*Lungs:* p. t. *Liver:* " " *Spleen:* " "	+ ++ ++
111	290	12 +	−30	Same as No. 110.	*Lungs:* p. t. *Liver:* " " *Spleen:* " "	+++ +++ +++
112	290	5 +	−30	Same as No. 110.	*Lungs:* p. t. *Liver:* " " *Spleen:* " "	+++ + ++
113	280	10 +	−20	Same as No. 110.	*Lungs:* p. t. *Liver:* " " *Spleen:* " "	++ ++ +
114	280	12 +	+70	*Lungs:* 1 or 2 nodules. *Liver:* several nodules. *Spleen:* " "	*Lungs:* p. t. *Liver:* " " *Spleen:* " "	+ + +
115	290	10 +	−30	Same as No. 110.	*Lungs:* p. t. *Liver:* " " *Spleen:* " "	+++ +++ +++

TABLE VII—*Continued.*

No. of animal.	Weight.	Duration of life.	Change in body weight after treatment.
Intravenous injection of 1 cc. of Liquid D every other week.			
	gm.		*gm.*
116	430	Healthy.	+260
117	260	"	+ 50
118	310	"	+130
119	370	"	+ 80
120	280	"	+180
121	270	"	+ 70
122	280	"	+ 60
123	320	"	+130
124	380	"	+130
125	220	"	+ 40

No. of animal.	Weight.	Duration of life.	Change in body weight.	Macroscopic changes.	Microscopic changes.	No. of bacilli.
	gm.	*wks.*	*gm.*			
126	330	22 ⊕	+140	*Lymph glands:* big as tip of small finger. *Lungs:* 1 or 2 nodules. *Liver:* 1 " 2 " *Spleen:* 1 " 2 "	*Lungs:* s. t. *Liver:* " " *Spleen:* " "	2 — 1
127	300	Same as No. 126.	+210	No marked change except central cheesy degeneration size of pea in lymph glands.	*Lungs:* c. t. *Liver:* " " *Spleen:* " "	1 — —
128	310	Same as No. 126.	+59	Marked hyperemia of internal organs. *Lungs, liver, and spleen:* 1 or 2 nodules.	*Lungs:* s. t. *Liver:* " " *Spleen:* " "	1 — —
129	360	Same as No. 126.	+100	*Lungs, liver, and spleen:* several grayish white protuberant nodules.	*Lungs:* c. t. *Liver:* " " *Spleen:* " "	— — 2
130	260	Same as No. 126.	+310	No marked changes.	*Lungs:* c. t. *Liver:* " " *Spleen:* " "	— 1 1

TABLE VII—*Continued.*

No. of animal.	Weight.	Duration of life.	Change in body weight.	Macroscopic changes.	Microscopic changes.	No. of bacilli.
	gm.	*wks.*	*gm.*			
131	350	Same as No. 126.	+190	No marked changes.	*Lungs:* c. t. *Liver:* " " *Spleen:* " "	— — —
132	310	Same as No. 126.	+290	No marked changes.	*Lungs:* c. t. *Liver:* " " *Spleen:* " "	1 — —
133	280	Same as No. 126.	+100	Same as No. 129.	*Lungs:* c. t. *Liver:* " " *Spleen:* " "	1 — —
134	310	Same as No. 126.	+180	*Lymph glands:* swelling size of pea. *Lungs:* inflamed. *Liver and spleen:* 1 or 2 nodules.	*Lungs:* s. t. *Liver:* " " *Spleen:* " "	— — —
135	350	Same as No. 126.	+40	*Lymph glands:* big as tip of small finger, central cheesy degeneration. *Lungs:* 1 or 2 nodules. *Liver:* no marked changes. *Spleen:* cheesy degeneration.	*Lungs:* s. t. *Liver:* " " *Spleen:* " "	— — —
136	250	13 +	−20	*Lymph glands:* swollen, large central cheesy degeneration. *Lungs:* inflamed. *Liver and spleen:* 1 or 2 nodules.	*Lungs:* s. t. *Liver:* " " *Spleen:* " "	3 2 1
137	230	16 +	−+	No marked changes.	*Lungs:* c. t. *Liver:* " " *Spleen:* " "	1 1 1

TABLE VII—*Continued.*

No. of animal.	Weight.	Duration of life.	Change in body weight.	Macroscopic changes.	Microscopic changes.	No. of bacilli.
	gm.	*wks.*	*gm.*			
138	290	14 +	−50	No marked changes.	*Lungs:* s. t. *Liver:* " " *Spleen:* " "	3 − −
139	300	16 +	−+	No marked changes.	*Lungs:* c. t. *Liver:* " " *Spleen:* " "	− − −
140	310	17 +	+90	No marked changes.	*Lungs:* c. t. *Liver:* " " *Spleen:* " "	2 1 6
141	300	15 +	+15	No marked changes.	*Lungs:* c. t. *Liver:* " " *Spleen:* " "	2 − −
142	260	15 +	−+	Same as No. 136.	*Lungs:* s. t. *Liver:* " " *Spleen:* " "	7 5 3
143	300	16 +	−+	Same as No. 136.	*Lungs:* s. t. *Liver:* " " *Spleen:* " "	1 − 2
144	280	15 +	−50	Same as No. 136.	*Lungs:* s. t. *Liver:* " " *Spleen:* " "	3 − −
145	310	11 +	−50	Same as No. 136.	*Lungs:* s. t. *Liver:* " " *Spleen:* " "	7 + 7
146	300	11 +	−50	*Lymph glands:* swelling size of pea. *Lungs:* grayish white nodules. *Liver:* grayish white nodules. *Spleen:* grayish white nodules.	*Lungs:* s. t. *Liver:* " " *Spleen:* " "	++ ++ ++

TABLE VII—*Concluded.*

No. of animal.	Weight.	Duration of life.	Change in body weight.	Macroscopic changes.	Microscopic changes.	No. of bacilli.
	gm.	*wks.*	*gm.*			
147	320	11 +	−40	*Lungs:* cheesy pneumonia. *Liver:* m. t. *Spleen:* " "	*Lungs:* p. t. *Liver:* " " *Spleen:* " "	+++ +++ +++
148	280	8 +	−30	*Lymph glands:* swollen, cheesy degeneration. *Lungs:* m. t. *Liver and spleen:* m. t.	*Lungs:* p. t. *Liver:* " " *Spleen:* " "	++ + +
149	270	14 +	−+	Same as No. 146.	*Lungs:* s. t. *Liver:* " " *Spleen:* " "	+ + +
150	280	14 +	−30	Same as No. 147.	*Lungs:* p. t. *Liver:* " " *Spleen:* " "	++ ++ +
151	280	16 +	−+	Same as No. 147.	*Lungs:* p. t. *Liver:* " " *Spleen:* " "	+++ +++ +++
152	250	22* +	+10	*Lymph glands:* swollen. *Lungs:* small nodules scattered between several grayish white protuberant nodules. *Liver:* the same. *Spleen:* the same.	*Lungs:* p. t. *Liver:* " " *Spleen:* " "	+++ +++ +
153	460	22* +	+50	No marked changes.	*Lungs:* p. t. *Liver:* " " *Spleen:* " "	+++ +++ +++

* These two animals died of the reaction arising from a sudden increase of the dose, which was doubled and which led to a marked development of the pathological processes.

scopic changes were present and progressive tuberculosis with a large number of tubercle bacilli. In the last four animals the action of Liquid D was not yet complete.

Nos. 152 and 153 were given twice the dose of the liquid in the 22nd week and died of the reaction 4 days later. On macroscopic examination the former

showed slight changes and the latter none. On microscopic examination the tissues surrounding the lesion were in a state of great congestion and masses of lymphatic cells as well as leukocytes were present. The lesions were surrounded by a new growth of granulation and connective tissue, but the centers showed cheesy degeneration.

In spite of the various obstacles to which the last series of animals had been subjected, the following results were obtained. Of 38 animals, 20 had remained apparently healthy for 22 weeks, when 10 were killed for examination, of which 6 exhibited indications of healed tubercular lesions, and 4 were in the suspended stage. Of the remaining 18 animals, 2 died in consequence of the reaction caused by the sudden increase of the dose of the preparation, and hence may be deducted from the total number. Of the 16 left, 4 showed traces of healed tuberculosis, 8 were in the suspended stage, and the remaining 4 in the progressive stage similar to the controls.

SUMMARY.

Judging from the macroscopic and microscopic study of the animals treated with the liquid, its action upon the tubercular lesions seems to be about as follows: The effect of a single injection upon the lesions is either negative or inconspicuous. But after repeated injections of the preparation the congestion and leukocytic infiltration about the lesions are markedly decreased, the cheesy material resulting from degeneration of the lesions and other degeneration products are in process of absorption, and young connective tissue is being actively produced in the periphery. While these changes are taking place the number of the bacilli is also being reduced until finally they can no longer be detected on microscopic examination.

Hence it appears that while the preparation may lack bactericidal action *in vivo* powerful enough to destroy all the bacilli at one injection, yet repeated infusions may nevertheless bring about the destruction of all the bacilli and the modification of the tubercular lesion into that of the suspended stage or even into the healed condition. Whether, therefore, the preparation brings about these results directly by killing the bacilli or indirectly by favoring the healing processes of the body, nevertheless it has power to inhibit the growth of or annihilate entirely the bacilli *in vivo*.

The experiments reported leave no doubt that Liquid D is capable of bringing about the healing of experimental tubercular lesions; but thus far that most important problem in chemotherapeutics, namely, the extent of the cure produced, has not been solved. The experiments indicate that sterility of the tissues as far as microscopic examinations go has been secured; but microscopic examination is not after all an absolute test of sterility.

In order to test this point, emulsions were made of the lungs, liver, spleen, and other organs of Treated Animals 134 and 135 (Table VII), and they were inoculated into the abdominal cavity of guinea pigs. Some of the animals receiving the emulsion developed tuberculosis, and therefore absolute sterility of the treated animals had not been obtained in these instances.

The problem of the destination and distribution of the preparation in the body of the treated animal, as well as its action against the tubercle bacilli, lesions, and the tubercular organs of the infected guinea pigs, is now being studied further with results to be reported at some future time.

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EXPLANATION OF PLATES.

PLATE 11.

FIG. 1. Control guinea pig (No. 111). All the nodules present a grayish yellow color and are transparent. They are more or less cirrhotic. The spleen is greatly swollen.

PLATE 12.

FIG. 2. Treated guinea pig (No. 113). All the nodules present a grayish white color. In the liver they are cirrhotic. The spleen remains small.

PLATE 13.

FIG. 3. Control guinea pig (No. 111). Tuberculous nodule in the liver. Leitz oc. 1, obj. 7.

a, focus of caseous degeneration; *b*, infiltrated layer; *c*, giant cells.

FIG. 4. Fibrous nodule in the lung of a treated guinea pig (No. 123). Leitz oc. 3, obj. 3.

a, nodule; *b*, parenchyma of the lung; *c*, calcareous deposit; *d*, glandular change of the bronchioles caused by chronic interstitial inflammation.

PLATE 14.

FIG. 5. Fibrous nodule of the liver of a treated guinea pig (No. 123). Leitz oc. 1, obj. 7.

a, nodule; *b*, lobuli hepatici; *c*, intrahepatic bile ducts; *d*, blood vessel.

FIG 6. Fibrous nodule of the spleen of a treated guinea pig (No. 123). Leitz oc. 1, obj. 7.

a, nodule; *b*, follicle; *c*, sinus venosus.

PLATE 15.

FIG. 7. Fibrous nodule of the inguinal glands of a treated guinea pig (No. 123). Leitz oc. 1, obj. 7.

a, nodule; *b*, follicle.

The above paper exceeds the limit of size set by the *Journal*. The reason for publishing it in spite of its length is found in the present importance of the subject of the specific treatment of tuberculosis to which the paper is a contribution.—THE EDITOR.

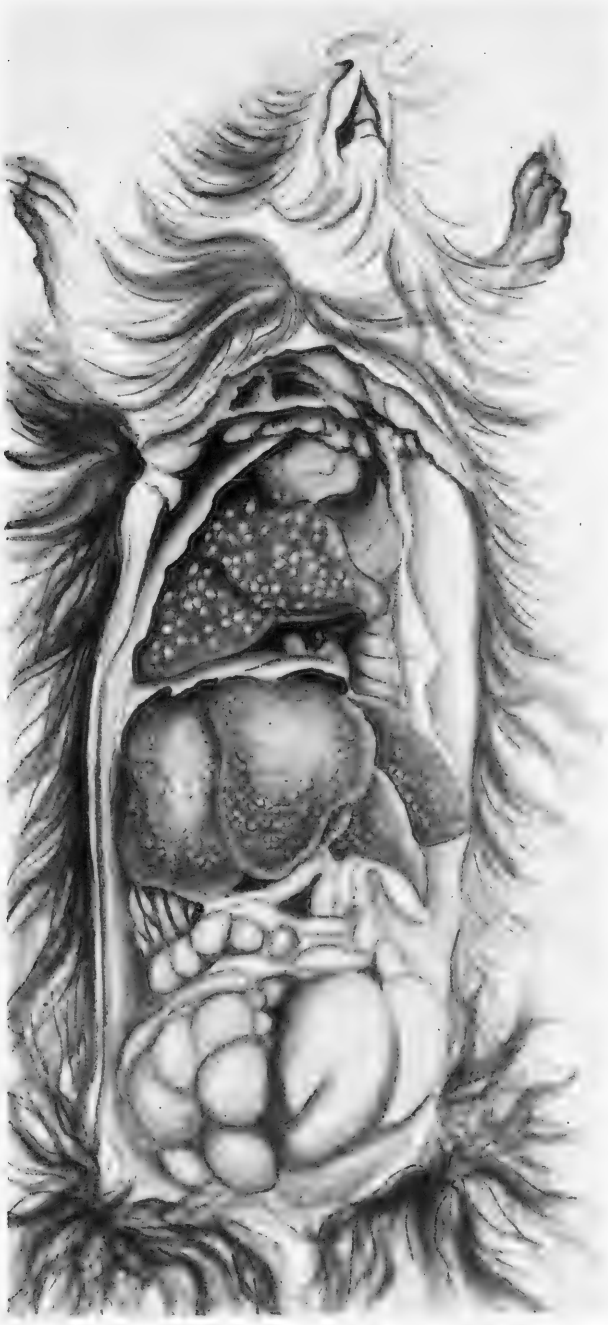

FIG. 1.

(Koga: Chemotherapy of Tuberculosis.)

FIG. 2.

(Koga: Chemotherapy of Tuberculosis.)

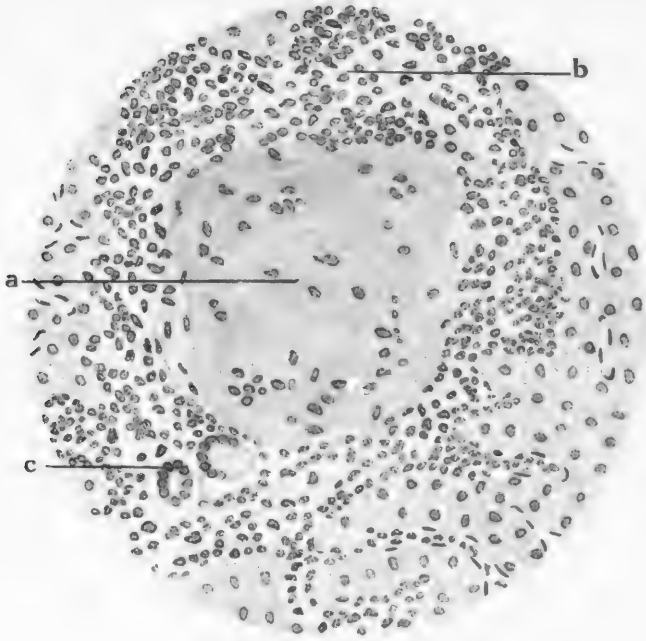

FIG. 3.

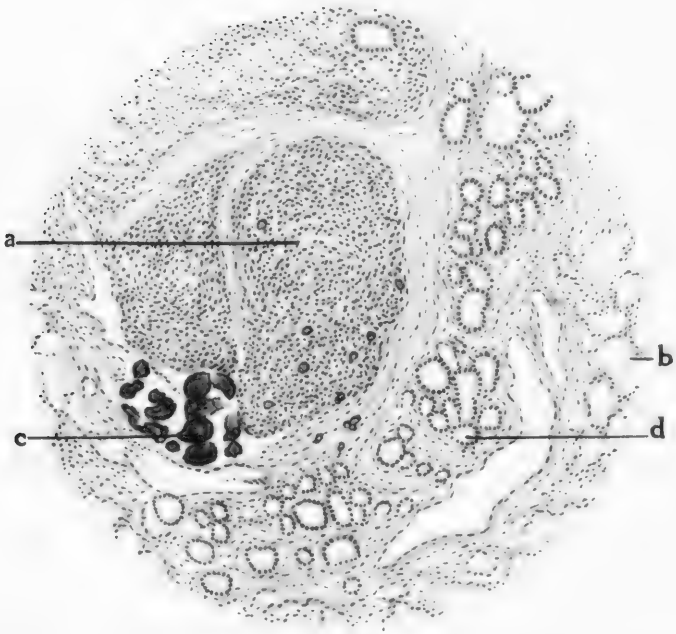

FIG. 4.

(Koga: Chemotherapy of Tuberculosis.)

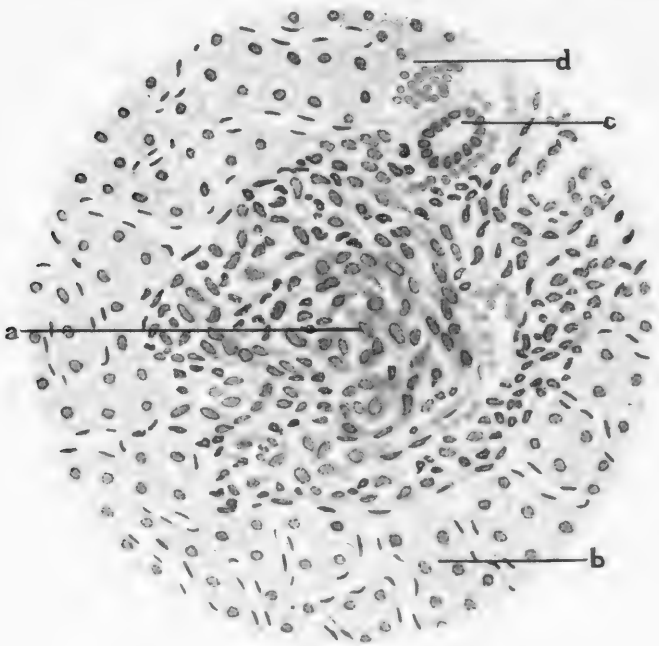

FIG. 5.

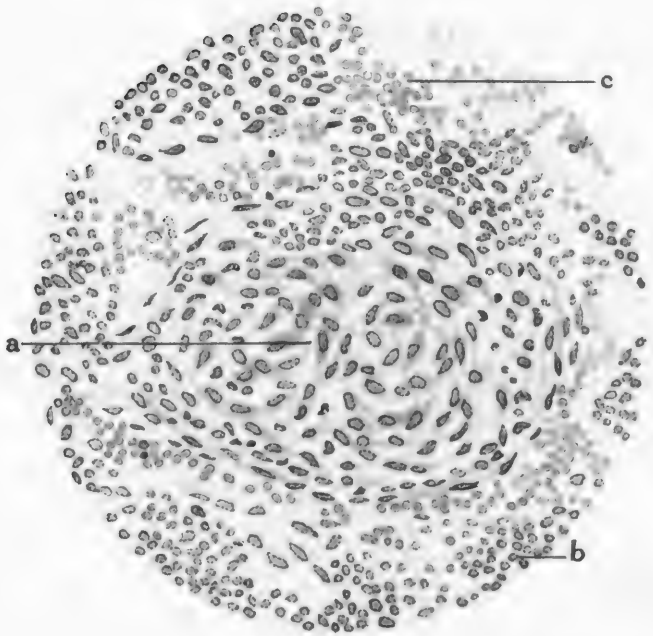

FIG. 6.

(Koga: Chemotherapy of Tuberculosis.)

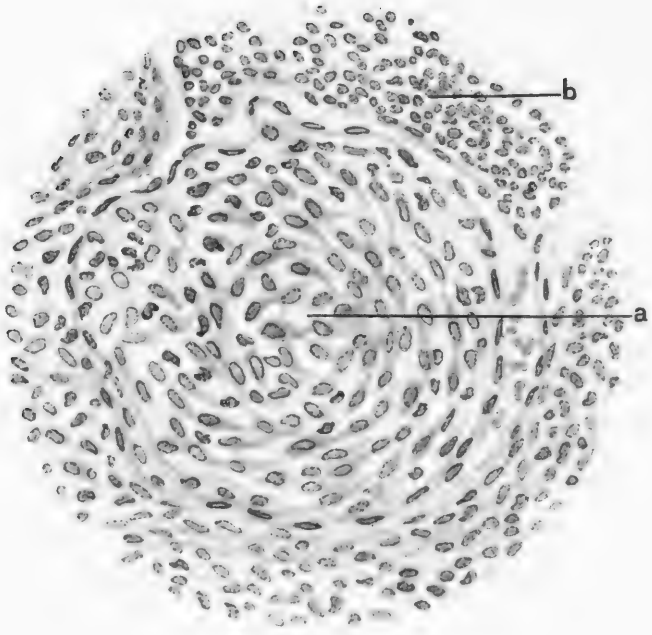

FIG. 7.

(Koga: Chemotherapy of Tuberculosis.)

A CONTRIBUTION TO THE CHEMOTHERAPY OF TUBERCULOSIS.

First Clinical Report.*

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(Received for publication, December 1, 1915.)

In the previous paper I have presented data on the specific chemotherapeutic treatment of experimental tuberculosis with my preparation of copper cyanide, called Liquid D. I desire now to present some of the results of the application of the treatment to human cases of tuberculosis. The treatment was first applied on September 26, 1914, at the Imperial Institute for the Study of Infectious Diseases, at which time Professor Kitasato was still its director. When he left the Institute on November 6 of the same year and established the Kitasato Institute for Infectious Diseases I followed him to the new institution where the treatment has been continued. In all, sixty-three treated cases are included in this report. The results have been tabulated as follows:

TABLE I.

The Treatment of Tubercular Patients with Liquid D.

	Total No. treated.	Cured.	Improved.	Died.	Treatment suspended.	Under treatment.
Non-active tuberculosis 1st stage.	19	13	2	—	1	3
Non-active tuberculosis 2nd "	6	3	3	—	—	—
Non-active tuberculosis 3rd "	4	1	3	—	—	—
Active tuberculosis 1st "	7	4	2	—	—	1
Active tuberculosis 2nd "	11	3	5	—	1	2
Active tuberculosis 3rd "	8	—	3	3	—	2
Surgical tuberculosis.....	8	1	4	—	2	1
Total.....	63	25	22	3	4	9

*The original paper in Japanese was read before the Alumni Meeting of the Kitasato Institute for Infectious Diseases, Tokyo, Apr. 4, 1915.

The term "cured" is applied to the cases that gained in body weight, showed temperatures below 37°C., no or nearly no physical signs, and bacillus-free sputum, though before treatment the sputum abounded in bacilli; and the patients did not complain and could attend to their regular work. This class of patients is being examined monthly at present in order to determine the permanence of the cure. The term "improvement" is applied to those cases that are still under treatment or in which treatment has been discontinued; they have gained in body weight, and show temperatures below 37°C., while bacilli are occasionally found in the sputum, and other symptoms are still present. "Under treatment" is applied to cases which are at the beginning of the treatment and in which the influence of the preparation is not yet evident. One of the patients classed as active tuberculosis in the second stage has passed into the third stage, in consequence of lack of nourishment preceded by hemoptysis.

I shall describe briefly the effect of the preparation upon the lesions and upon the patients, before reporting the typical cases.

Influence of Liquid D upon the Lesions.

In one case of acute progressive pulmonary tuberculosis, which had been negative to the von Pirquet test, the preparation produced no effect. But in other cases of pulmonary tuberculosis, there appeared, on the day following the injection, dullness accompanied by râles; if the dullness and râles were present before treatment, the former became more distinct, and the latter increased. These changes are indicated in the chest charts (Cases 7 and 9), and they disappear or diminish on the 8th or 9th day after the injection. By repeated injections the regional reactions gradually disappear or diminish, but by increasing the dose of the preparation they reappear. With each successive disappearance of the signs physical regional phenomena also diminish, until finally they disappear altogether. The dullness at the site of the old lesions does not always disappear; sometimes it is converted into a short tympanic sound. In a few cases the dullness as well as the râles diminish or disappear immediately after the first injection. In Case 2 and in five other cases it was difficult to detect the regional sign before injection, but on the day following the injection râles and dullness appeared by which the lesions could be easily detected, as is depicted in the chart. From these reactive phenomena, as well as from the animal experiments, we have concluded that congestion occurs in a high degree about the lesion immediately after the injection of the preparation. However, in four cases in which bloody expectoration was present, the preparation produced no injurious effect upon the bleeding; and in two of the

four bleeding ceased on the day after the injection. The cases in the third stage generally show stronger reactions, which sometimes last as long as 2 weeks.

In cutaneous tuberculosis a local hyperemia and edema arise in a few hours after the injection. In one case pustulation of the lesion was observed 24 hours after injection. These reactions usually disappear in from 8 to 9 days, and at the same time the lesion diminishes greatly in size. With repetition of the dose the reactions diminish until at last they do not appear at all. Therefore, the minimum dose should first be given, and increased by 0.5 mg. each time subsequently. In this way the same degree of reaction may be obtained each time.

Five cases of tuberculosis of the lymphatic glands have been treated. One patient suffered from slight pain at the site of the lesion, but no swelling was observed. After two injections the lesion was completely absorbed. One case suffered from severe pain immediately after the injection. The gland became swollen considerably and ulcerated on the 2nd day. The remaining three cases suffered from swelling in the region of the gland, and pain on the following day, which disappeared in 7 to 8 days. In two of the three patients, four injections have led to the complete absorption of the lesion, while in the remaining case a hard nodule the size of the tip of the small finger, and feeling like cartilage, remains.

In one case of tuberculosis of the kidney (Case 3), the upper part of the left kidney was found on palpation to be swollen to the size of the fist. On pressure hyperesthesia and hematuria were observed. The latter ceased on the 2nd day, while the swelling and pain disappeared on the 7th day after injection. With the subsidence of the pain at the time of urination, the urine became markedly clearer than before treatment. Unfortunately the patient ceased to come for treatment after the second injection.

One case was suffering from vertebral caries with open suppuration accompanied by pulmonary tuberculosis in the first stage and tuberculosis of the lymphatic glands. The patient complained of oppressive feeling in the breast cavity after each injection. After twelve injections the patient was relieved of discomfort and was able to return to work.

In two cases of intestinal tuberculosis, the injection brought about a temperature of 40°C. with ten to twenty bloody mucous diarrheal stools 3 days later. These phenomena disappeared in 2 days. Three more cases of intestinal tuberculosis were subjected to the special precaution of evacuating the contents of the bowels beforehand, and thus these inconveniences were avoided.

Eighteen cases that had been receiving tuberculin and vaccine treatment according to Shiga's method showed neither local reactions nor rise of body temperature. The duration of the disease was considerably shortened. Case 6 is typical of these cases.

Influence upon the Tubercle Bacilli in the Sputum.

A bacteriological examination was made of the first sputum expectorated each morning in six cases in the second and third stages. The results have been recorded according to Gaffky's table and arranged diagrammatically in curves (Text-figs. 1 to 6).

In Case 2 a remarkable increase was observed from the day following injection. The climax was reached on the 10th day. From the 11th day, however, a gradual decrease was noted, and negative results were obtained on the 14th day. On the second injection of the preparation and afterwards, a slight increase was observed each time, but from the 10th day a decrease was noted. At present negative results are always obtained even after the injection. In Case 3 the decrease was observed immediately after the injection. Negative results were obtained in 2 weeks. The patient ceased to receive the treatment after that day, and has not reported since. In Case 5 the decrease was observed immediately after the first injection. Negative results were obtained from the 8th to the 14th day, when the second injection was given. On the day following the second injection, an increase to No. II of Gaffky's table was observed, but on the 3rd day negative results were obtained. Since that time two injections have been given with negative results on each examination. In Case 8 innumerable bacilli appeared on the day following the injection, but they decreased to Gaffky's No. II on the 14th day. The second injection again resulted in the appearance of innumerable bacilli. A remarkable decrease was observed from the 9th day, and at last on the 14th day negative results were obtained. From the day following the third injection a gradual increase was observed until the climax was reached on the 9th day. Since then a gradual decrease has been noted, and negative results were obtained on the 14th day. Each examination after that gave a negative result, although five injections have been made. Case 9 was in the third stage of pulmonary tuberculosis. On the 3rd day after the first injection a great increase in the number of bacilli was observed. From the 5th day they decreased, but on the 11th day innumerable bacilli were observed for the second time. They decreased on the following day. After the second injection a gradual increase of the bacilli was noted, and no decrease was observed. The fourth and the fifth injections had no effect. The physical phenomena grew worse, the temperature curve did not fall, and the fever reaction became permanent. No further treatment was given on account of weakness. Case 10 also belonged to the third stage. On the 3rd day after the first injection, innumerable bacilli appeared, but on the 5th day a gradual decrease was observed. On the 9th day negative results were obtained, but from the 10th to the 14th day innumerable bacilli were again observed. The results of the examination on the 13th day were negative, as the material for examination was unsatisfactory, and they are therefore not given in the chart. The second injection gave a better result, and the third resulted in a slight increase on the day following the injection.

A gradual decrease was observed and a negative result finally obtained. After that four injections were always given, the dose being increased each time. The dose was then decreased slightly, and at present a negative result is nearly always obtained.

The film method of bacteriological examination of the sputum is liable to error, for the concentration of the specimen, the thickness of the film, and the material selected produce different results. The more exact antiformin treatment of the sputum is, therefore, to be preferred. As the examination of the first morning expectoration for several days in succession gives important data as to the effect of the preparation, I chose certain cases upon which these successive examinations were carried out. The results were found to correspond with the changes of the local reactions and the temperature curves. One of the phenomena that should be especially noted is that a patient in the first stage of pulmonary tuberculosis who ejected no bacilli in the first sputum on the day of the injection, often passed as many bacilli as correspond to Gaffky's Nos. II and III on the 2nd and 3rd days after the injection. To a patient in the third stage of the disease, a large dose either exceeding or the same as that given to a patient in the first or second stage results only in an intensification of the symptoms or an increase in the number of bacilli. Changes in the form of the bacilli were observed on the 2nd or 3rd day after the injection. The bacilli will then present the following three varieties: (*a*) the granules in the bacilli become indistinct and thus the interior becomes somewhat homogeneous; (*b*) the bacilli which have divided into several sections resemble streptococci; (*c*) the bacilli which have collected in large masses resemble staphylococci.

The three degenerated forms of the bacilli are often visible when cavities are present in the lung or the specimen has been overheated for staining purposes, and special precautions must therefore be taken before the examination is made. If the bacteriological examination of the patient in the first stage shows that the bacilli in the sputum are normal, the bacilli of the same case after the first injection will be degenerated forms similar to those often discovered in the sputum of patients having lung cavities. It may be conjectured that this degeneration in the form of the bacilli is produced by the injection

of the preparation. The sputum will, however, contain normal bacilli again 5 weeks after injection. The transformation gradually sets in, beginning with the 2nd or 3rd week.

Influence upon Body Temperature.

In more than twenty cases in which the body temperature ranged between 37° and 38°C. before injection, the temperature subsided completely after one or two injections and did not rise again above 37°C., as shown in the temperature curve of Case 1.

The curve of Case 4 shows that the temperature which previously ranged between 38° and 39°C. gradually fell after the first injection, and after the second did not rise above 37°C. This was a case of pulmonary tuberculosis in a woman in the third stage, with great weakness. She showed general improvement in consequence of the reduced temperature, and was therefore dismissed from the hospital. Unfortunately she had a chill the same night and her temperature rose to 40°C., due to a pneumonic attack, which subsided after complete rest, the temperature falling again to 38°C. The lesion, however, was observed to have extended considerably. The third injection brought about no improvement, and the patient died of debility. From this it will be seen that patients suffering from pulmonary tuberculosis in the third stage should be kept quiet for a period of 2 weeks after the injection. In three cases in which there had been no rise of temperature, it rose to 38–39°C. after slight exercise within 3 or 4 days after the injection. A localized pneumonic attack also occurred in these cases, but subsided after rest of about 3 days. Hence I emphasize the fact that in cases of slight pulmonary tuberculosis the patients must be kept quiet for 3 to 4 days after each injection.

Case 3 had a febrile attack on the 3rd day after the first injection (the dose being 16 mg.), in spite of having been kept quiet. After the second injection (same dose) the temperature rose only to 37.7–38°C., and the third injection (15 mg.) was not followed by fever.

Case 8 was given 15 mg. for the first injection. The temperature became normal.

Case 9, as already described, had a severe local reaction.

Case 10 was one of pulmonary tuberculosis in the third stage, the temperature reaching 39.8°C. Three injections of 16 mg. each were given, followed by a normal temperature and improvement of the physical signs. The bacilli in the sputum became considerably less. With the hope of accelerating the favorable effects 17 mg. were given for the fourth injection. There followed increase of the bacilli in the sputum and rise of temperature above 38°C. After 3 weeks' rest in bed the temperature fell to normal, after which the fifth and then the sixth injection, each consisting of 16 mg., were given. The temperature remained normal, the physical phenomena improved, and the bacilli in the sputum almost

disappeared. As a result of this experience we believe that the dose and the interval between each two injections should be governed by special precautions. Reduction of the dose to 13 mg. in cases suffering from pulmonary tuberculosis in the third stage, and in cases of spreading pulmonary tuberculosis followed by pleurisy (Case 9), produce, as a rule, no rise of temperature, but rather a reduction to normal. Drs. Otani, Okawara, and Yabe are carrying on clinical observations of various kinds in the Kitasato Institute, in order to learn the variety and nature of the reactions and the manner of their control. I have also asked more than twenty specialists in Japan to use my preparation, and reports from these sources may therefore be looked for. In three cases the temperature began to rise on the 10th day after each injection. It has not yet been determined whether the next injection in these cases should be made on the 11th day.

Influence upon Body Weight.

During the 3 days after injection, decrease of the body weight, amounting to 0.5 to 1 kilo, was observed in cases of the first or second stage. But before the next injection, or in 11 days, the weight will again rise to the point present before the injection, and usually even higher. However, with the cases showing a certain intensity of reaction, or in the third stage, the loss following the injection may not be regained. This result might perhaps be avoided, if more time were allowed between each two injections. Among the sixty-three cases which I have treated, a loss of weight has been observed in six only, while all the rest gained more or less.

Influence upon the von Pirquet Reaction.

Three cases in which the von Pirquet reaction was fading were given the preparation with the result that the regional infiltration reappeared and swelling was produced. In one case a blister was formed, which disappeared in 2 or 3 days. This phenomenon may indicate that the preparation has a certain action upon the toxin of the tubercle bacillus.

Thirteen cases that had given positive von Pirquet reactions were reexamined from 2 to 3 months after the disappearance of all clinical and bacteriological signs, and all were negative.

Influence upon the Subjective Symptoms.

A marked improvement is often produced in cases of pulmonary tuberculosis in the first or second stage, while in the third stage severe fatigue is felt for 3 or 4 days. Sometimes cases in the first or second stage also suffer from fatigue. At the same time a slight flush or night sweat may result, which disappears in 2 or 3 days.

Directions for the Use of the Preparation.

As a result of the experimental tests in animals on the toxicity of the preparation, I have come to the conclusion that 0.6 gm. may be introduced without injury into the veins of a man weighing 60 kilos. Moreover, it was found that a dose sufficient to establish complete cure in the experimental tuberculosis of the guinea pig is 0.5 mg. per 500 gm. of body weight. Hence, a curative dose of the preparation for a man seems to be 0.1 gm. The great difference in the species of animals was, of course, taken into consideration, and therefore in the beginning I gave a dose of 10 mg. to human cases.

Dr. Kojima, who had been suffering from pulmonary tuberculosis for 10 years, offered himself for the first trial of the preparation; he developed ileus and strangulation of the intestine and died before the influence of the preparation could be seen. The test proved, however, that in the dose employed the preparation was non-toxic for man.

The preparation is colorless, transparent, and of neutral reaction. If allowed to stand in the air for more than 6 hours, crystallization sets in. It must therefore be used as soon as the ampules are opened.

The preparation is highly irritating to the tissues and hence neither subcutaneous nor intramuscular injection can be employed and it must be injected exclusively into a vein. Injected into the subcutaneous tissues or muscles it causes severe pain and swelling. After injection the patient must be kept absolutely quiet in bed until the reactions disappear. As a rule, 3, 7, and 14 days are the periods during which patients in the 1st, 2nd, and 3rd stages, respectively, of pulmonary tuberculosis must keep quiet. Extreme emaciation is a contraindication to the employment of the preparation.

Rest of the organs affected by tuberculosis is also necessary; *e.g.*, the lessening of the amount as well as the choice of food in intestinal tuberculosis, the application of narcotics for the prevention of hemoptysis in pulmonary tuberculosis, the application of narcotics for the purpose of decreasing cough and limitation of speech in laryngeal tuberculosis, production of artificial pneumothorax (probably) in pleural tuberculosis, and application of splints for surgical tuberculosis.

Rest is necessary because the injection causes local congestion and

therefore bleeding may occur; but, on the other hand, the injection has been shown to increase the coagulation of the blood, and consequently hemorrhage will stop if rest is maintained. The injection should be made slowly, otherwise it may cause acceleration of the heart action and giddiness.

Dose.—The primary doses for the various stages and types of tuberculosis are as follows:

	mg.
Pulmonary tuberculosis in the 1st stage	14–16
" " " " 2nd "	12–14
" " " " 3rd "	8–12
Intestinal tuberculosis	8–12
Laryngeal "	8–12
Pleural "	8–12
Peritoneal "	8–12
Tuberculosis of lymphatic glands	15–17
" " bone	15–17

The doses for cutaneous tuberculosis should be increased each time by 0.5 mg. from the second injection. For laryngeal tuberculosis, however, decreasing by 0.5 mg. after the second injection is better. For other types of tuberculosis the problem of whether to increase or decrease, to repeat the increase and decrease, or to maintain the same dose is still to be worked out.

When the fever reaction lasts more than 2 weeks, it may often be reduced by lessening the doses by 1 mg. for the subsequent injection.

For pregnant women a little smaller dose should be given.

In intestinal tuberculosis purgatives must be given on the day previous to the injection.

An interval of a fortnight has been regularly allowed in every case. I have had no instance in which even a small amount of the preparation was injected at shorter intervals.

The preparation is affected by phenol and lysol. Therefore the skin and syringe must not be disinfected with these solutions. The instruments must be disinfected by heating, then dipping in alcohol, and washing carefully with physiological saline solution. The skin should be disinfected with tincture of iodine and alcohol.

Internal administration of apricot juice will increase the free prussic acid in the body, and it should therefore not be given with the preparation. Creosote and its derivates and potassium iodide sometimes produce fever and other ill effects.

Fastness of the Bacilli.—An emulsion of the organs of Treated Animals 134 and 135,[1] which had been receiving injections of the preparation, was introduced into the peritoneal cavity of a guinea pig. Tuberculosis of the intestine and spleen, with nodule formation, was produced. By injecting Liquid D, the nodules were made to disappear. I observed a case in which the preparation was given intravenously over twenty-one times to a patient who is now improving. These facts may show that the preparation probably brings about no fastness in the tubercle bacilli.

Brief Case Reports.

Case 1.—T. F., female, aged 18 years. No information obtained about grandparents, who died when she was a child. Her father died of beri-beri in his 40th year; mother living; three brothers and sisters, one of whom died of a disease of which she knows nothing. No tendency to tuberculosis seemed to exist. She had always been healthy and free from severe illness, except diphtheria, which she contracted in her 7th year. She suffered from a slight swelling and tenderness of the bowels in Apr., 1914. The condition, which was diagnosed by the attending physicians as peritonitis, subsided in about a month. She had been well since then until the middle of Oct., 1914, when she caught cold and suffered from fever and cough.

Diagnosis.—Pulmonary tuberculosis in the second stage; serous pleurisy on left side.

Present Illness.—Weak constitution; malnutrition; skin not dry, elasticity normal; poor in subcutaneous fatty tissue; face pale; conjunctiva anemic; larynx slightly red; no swelling in the lymphatic glands of the neck; typical pigeon chest; breathing weak on the left side; percussion sound short within the region of four fingers' breadth at the apex on the right back; left lung, dullness below the third rib; on the left frontal apex and right lateral apex râles were heard; respiration weak, lacking in the vocal vibration; bowels normal; pleural lymphatic glands, no swelling or tenderness; body weight 33.2 kilos. Von Pirquet reaction, +, +, +.

Progress.—On Nov. 10, 1914, 15 mg. of the preparation were injected intravenously. From the following day the fever subsided and the general condition improved. The bacilli correspond to Gaffky's No. II. Since then twenty injections have been given. At present the patient weighs 35.2 kilos; has a dullness over the right apex; and the sputum is free from tubercle bacilli.

Case 2.—K. K., male, aged 29 years. Parents and six brothers and sisters all living and healthy; no congenital tuberculosis. Has always been weak and

[1] Koga, G., *J. Exp. Med.* 1916, xxiv, 107.

neurasthenic, but has had no severe illness except colds. 4 years ago he swallowed a piece of metal, which was removed by operation. 2 years ago a diagnosis of tuberculosis of the right apex was made. At that time the temperature was above 37.4°C., and negative results had been obtained by bacteriological examination of the sputum. Under clinical treatment all the symptoms subsided in about 3 months. In Jan., 1914, he suffered from a febrile attack, the temperature reaching as high as 38°C., with pain in the left thorax. Toward the end of the month, the fever reached 40°C. with accompanying expectorations, cough, and night sweats. Appetite unimpaired; stools once daily.

Diagnosis.—Pulmonary tuberculosis in the second stage.

Present Illness.—Constitution medium; nourishment good; skin not wet; features anemic; cheeks slightly flushed; conjunctiva anemic; no white membrane over the tongue; neck a little long; lymphatic glands of the neck not swollen; thorax normal in form; breathing weak along the left side of the thorax; by percussion on left upper lobe, above the line corresponding to the second intercostal space, dullness is observed; on auscultation râles are heard over this area; right upper lobes, bronchial sound; at the apex of the heart and left axillary region slight friction; general respiratory sounds coarse; dullness over the region of the heart; heart normal in size; heart sounds also normal; all organs in the abdominal cavity normal; urine showed no casts or albumin. Von Pirquet reaction, ++, ++, +. Bacilli correspond to Gaffky's No. IV. Body weight 53.3 kilos. Temperature 37.4°C.

Progress.—Received intravenously 16 mg. for the first time on Feb. 26, 1915. On Feb. 28 febrile reaction reaching 38.3°C. On Mar. 3 it reached as high as 39°C. Afterwards it fell to 37.6–37.7°C. The behavior of the bacilli in the sputum is shown in the chart; after an interval of 2 weeks the second injection was given. The temperature began to fall, the highest being 37.3°C. Six more injections each at intervals of 2 weeks were given. At present the temperature is 37°C. On the left side of the intercostal space one or two râles are heard; no dullness or bronchial respiration along all the remaining regions of the lungs. The bacilli correspond to Gaffky's No. II. The patient is still receiving the injection. Body weight 53 kilos.

Case 3.—T. Y., male, aged 25 years. Both parents healthy; three brothers and sisters living; two brothers died of consumption. The patient has never been strong. 3 years ago he caught cold and suffered from cough and expectoration, and very severe night sweats and fever, which improved considerably under the use of the preparation for 4 months. From Nov., 1914, a renewed attack of fever was observed. He suffered this time from hematuria; urinated fifteen times in 24 hours. He also had a severe pain at the opening of the urethra and in the lower bowels. At that time he urinated over seventeen times daily. Appetite impaired.

Diagnosis.—Catarrh of the left apex and tuberculosis of the left kidney.

Present Illness.—Constitution and nourishment impaired; skin dry; features emaciated; conjunctiva highly anemic; pulsation 110, weak; neck long; no swollen lymphatic glands; thorax symmetrical; breathing slightly weak on the left side; on percussion over the left frontal region of the lung there were dullness down to the third rib, and bronchial respiration and metallic respiratory sounds; over the whole region of the upper lobe of the left lung there were slight râles; normal precardial dullness; anemic heart sounds; left kidney slightly tender and impalpable; bladder not tender; the bacilli corresponded to Gaffky's No. III. The tubercle bacilli in the urine were moderately numerous. Urine neutral and slightly cloudy; considerable deposits were obtained by centrifugalization; albumin in the filtered liquid; no epithelial cells visible under the microscope. Von Pirquet reaction negative. Weight 35.4 kilos. Urine 1,450 cc.; urinated fifteen times daily.

Progress.—On Feb. 9, 1915, 15 mg. of the preparation were injected intravenously. On the following day the left kidney was found to be tender and as large as the fist. The urine assumed a red color, erythrocytes being present; amount 1,700 cc.; urinated fourteen times. On Feb. 11 the pain in the lower bowels and at the urethral opening at the time of urination disappeared, while the urine became somewhat limpid. The deposit obtained by centrifugalization was examined microscopically, and tubercle bacilli were demonstrated. The symptoms in the lungs showed no conspicuous changes. The bacilli in the sputum are shown in the chart. Since that time the urine increased to 2,000 gm. He left the hospital and has not reported since.

Case 4.—I. O., female, aged 19 years. Father died of stomach trouble; mother and one younger brother living. No evidence of an inherited tendency toward tuberculosis. She had been healthy without any noteworthy illness since birth. She suffered from cough and night sweats since Dec., 1914. Menstruation irregular; appetite impaired; sleeps well.

Diagnosis.—Pulmonary tuberculosis in the third stage, and on the right side tubercular pleurisy.

Present Illness.—Constitution good; nourishment impaired; features agonal; cheeks flushed; conjunctiva highly anemic; skin dry; tongue has no white membrane; pulse weak, count over 105 per minute; temperature 38.1°C.; thorax symmetrical; respiration weak on the right side; right lung shows bronchial respiration down to the fourth intercostal space; right side of the back has a short sound, and on auscultation bronchial sounds with râles; right apex measures 4 by 3 cm.; normal precardial dullness; heart normal; lower bowels somewhat distended; axilla is tender, but has no dull percussion sound; no hypertrophy of the intestinal walls or lymphatic glands occurs. Von Pirquet reaction, +, +, −. The bacilli correspond to Gaffky's No VII. Body weight 43.8 kilos.

Progress.—Received intravenously 16 mg. of the preparation on Feb. 16, 1915. The body temperature fell to 37.5°C. on Mar. 1. General condition improved. Received the second injection of 16 mg. on Mar. 3. The temperature rose to 38.1°C. and fell again to 37.1–37.2°C. on the following day; general conditions

improved markedly. She was dismissed from the hospital on the 6th day after the second injection. On that evening fever set in which rose to 39.8°C. at 9 o'clock, caused by overexercise. Since that time emaciation became conspicuous, and the temperature curve became irregular. She was again admitted to the hospital. The third injection was given on Mar. 19, and the fourth on Apr. 7, each time the doses being 16 mg. No reduction of fever was produced. Appetite poor. Died on Apr. 28.

Case 5.—M. K., male, aged 27 years. Both parents healthy. No inherited tendency to tuberculosis could be traced. He contracted measles in his 2nd year, but besides this he has had no marked sickness until 4 years ago when he suffered from an external wound and a broken right fifth rib, followed by an attack of pleurisy which yielded to medical treatment. 2 months ago hemoptysis (about 299 cc.) occurred. Since then he has had several hemorrhages. He is suffering from cough, with moderate expectoration, but no night sweats. Appetite good. Stools once daily.

Diagnosis.—Pulmonary tuberculosis in the second stage; right tubercular pleurisy.

Present Illness.—Constitution and nourishment good; conjunctiva not anemic; pulse regular, 84 per minute; no jugular lymphatic gland swelling; thorax symmetrical; breathing weak on right side; on auscultation râles were heard; at the frontal border line between the right lung and the liver an inspiratory bronchial sound was heard; on the back corresponding to the lower margin of the scapula a short friction sound; the left apex had a short sound at the region corresponding to the fossa supraclavicularis; normal precardial dullness; heart sounds also normal; no change in the bowels. Von Pirquet reaction, +, +, +. The bacilli correspond to Gaffky's No. V. Temperature 37.5°C. Weight 49.1 kilos.

Progress.—The first intravenous injection of 16 mg. of the preparation was given on Jan. 8, 1915. A night sweat occurred the same night. On the following day along the border line between the right lung and the liver numerous râles were heard, but the friction sound on the back of the right lung disappeared; during the night of Jan. 12 he suffered from pulmonary hemorrhage (about 30 cc.). Since that night until Jan. 22 he has had several hemorrhages; bloody sputum was expectorated until Jan. 29. Therefore the second injection was postponed until Feb. 2, when 16 mg. were again given intravenously. The general condition showed great improvement. The third injection (16 mg.) and the fourth (17 mg.) were given on Feb. 18 and Mar. 5, respectively. The symptoms in the lung disappeared completely, and the sputum was free from tubercle bacilli. Subjective symptoms also subsided. Body weight increased to 49.8 kilos.

Case 6.—M. J., male, aged 34 years. Father died of heart disease; mother living. Has no paternal uncles or aunts; three maternal uncles and aunts, one of whom died of carcinoma. Three brothers and sisters. His elder brother died of tuberculosis and his nephew is also suffering from it.

He has been weak since birth, but has contracted no serious disease. In Apr., 1915, he was found to be suffering from pulmonary tuberculosis. Since that

time he has been receiving tuberculin treatment. At present has no subjective symptoms.

Diagnosis.—Pulmonary tuberculosis in the second stage.

Present Illness.—Both constitution and nourishment good; skin and mucous membrane give no sign of anemia. Larynx somewhat reddened; no swelling in the jugular lymphatic glands; thorax symmetrical; breathing also symmetrical. In the left lung short percussion sound down to the third rib in front and the lower edge of the scapula on the back; these regions had a weak respiratory sound while at the apex a bronchial respiratory sound was heard; the right apex has a short sound over a radius of four fingers; normal precardial dullness; bowels normal; temperature 36.9°C. Bacilli in the sputum correspond to Gaffky's No. I. Weight 36.3 kilos.

Progress.—The first intravenous injection of 16 mg. was given on Nov. 10, 1914. The left apex had a dull percussion sound, and râles appeared. Weight on Nov. 24, 36.3 kilos. On the same day the second injection of 16 mg. was given. Weight on Nov. 26, 35.8 kilos; on Dec. 8, 36.1 kilos. On Nov. 8 he had only a very weak respiratory sound at the left apex; all other symptoms absent. On Jan. 12, 1915, he was examined, but had no symptoms. The sputum also was found to be free from bacilli. On Apr. 9 body weight was 47.5 kilos. Von Pirquet reaction negative. No physical phenomena were present in the lung. No subjective symptoms.

Case 7.—S. K., male, aged 36 years. Father and mother both died of stomach trouble at 71 and 67 years, respectively. Six brothers and sisters, one of whom died of tuberculosis; the rest are living. One maternal relative is suffering from tuberculosis.

He has never been strong. In his 7th year he contracted peritonitis, which was cured in 2 months; had beri-beri in his 20th year and ever since has been suffering from cerebral neurasthenia; 6 years ago a diagnosis of tuberculosis of the apex was made, although he had no cough or expectoration; the following year climatic and tuberculin treatment were tried; he says he is susceptible to colds; at present little expectoration. Appetite normal; stools once daily.

Diagnosis.—Pulmonary tuberculosis in the second stage.

Present Illness.—Both constitution and nourishment poor; skin and mucous membrane anemic; larynx somewhat reddened; neck long; no swelling of the jugular lymphatic glands; thorax flat; the region of the manubrium sterni sunken; breathing weak on both sides; in the upper lobes of both lungs a very weak respiratory sound is present; at the right apex there is a bronchial sound; no change is perceptible by percussion; normal precardial dullness; no anemic sounds; bowels sunken, but no change is perceptible. Von Pirquet reaction, +, +, +. Tubercle bacilli in the sputum can only be demonstrated by the use of antiformin. Weight 42.8 kilos. Temperature 36.8°C.

Progress.—The first injection of 16 mg. was given on Jan. 19, 1915. On Jan. 20 the right apex had a short sound on both sides down to the third rib, where many râles were heard. Cough and expectoration present. The bacilli in the

sputum correspond to Gaffky's No. II. The second injection of 16 mg., the third of 17 mg., and the fourth of 17 mg., were given on Feb. 2 and 16, and Mar. 2, respectively; bronchial respiratory sounds at the right apex and a few râles at the left scapular region appeared on May 7, when the fifth injection of 16 mg. was given. On May 20 the body weight was 44.5 kilos. The râles had all disappeared; only the coarse respiratory sound of the right apex remained. The injection was, therefore, suspended.

The results of five sputum examinations were negative.

Case 8.—Y. I., male, aged 36 years. Father died of stomach trouble at 59 years of age, and mother died of pneumonia in her 56th year. Has six brothers and sisters, all of whom are healthy; wife and five children living; one child died immediately after birth. No inherited tendency toward tuberculosis could be established.

He has always been healthy; suffered from enteric catarrh in his 18th year; and from typhoid fever in his 28th. In Apr., 1914, contracted laryngeal tuberculosis; in August had fever, cough, and expectoration; a tender tumor as large as the tip of the little finger appeared at the anal region; it was operated on and is still excreting pus; since then all the symptoms have been worse; emaciation setting in; night sweats slight; appetite impaired.

Diagnosis.—Pulmonary tuberculosis in the second stage; left axillary lymphatic tuberculosis and tubercular ulceration at the anal region.

Present Illness.—Constitution poor; nourishment impaired; skin yellowish brown and somewhat anemic; conjunctiva anemic; larynx slightly congested; neck short and no swelling in the lymphatic glands; thorax symmetrical; breathing symmetrical; in both lungs dullness up and down the borders of the scapula; many râles were heard down to the second intercostal space; back of the left lung general prolongation of exhalation; swelling of the lymphatic glands of the left side; the left axillary glands were swollen to about the size of a pigeon's egg; tender, but no adhesions; normal precardial dullness; bowels normal; ulceration as large as a pea at the anal region; the edges show gradual transition, but no new growth of the mucous membrane; pus is present. The bacilli in the sputum correspond to Gaffky's No. VI. Von Pirquet reaction, +, +, −. Weight 46.5 kilos. Urine free from albumin and casts.

Progress.—The first injection of 15 mg. was given on Jan. 16, 1915. Severe sweats occurred that night, but subsided in 2 days; on Jan. 24 no râles were heard; on Jan. 29 the second injection of 16 mg. was given. That night a slight pain was felt at the left axillary glands; by massaging the region the swelling disappeared; the excretion of pus from the anal lesion ceased; a slight increase of expectoration was noted; the third injection of 16 mg. was given on Feb. 12, and fever subsided completely. All the clinical symptoms had gone except the short percussion sound at the left apex. The temperature and the results of bacteriological examination of the sputum are shown in the chart. Since then the sputum was examined several times under the microscope, but negative results were obtained. Weight 48.3 kilos.

Case 9.—A. Y., female, aged 26 years. Father died of consumption; mother still living. One paternal uncle died of apoplexy; maternal uncles and aunts are all healthy; has three brothers and sisters, all of whom are healthy. Husband and two children also healthy.

The patient has been healthy since birth until Apr., 1914, when she had a hemorrhage; since then she has had five hemorrhages; case diagnosed as pulmonary tuberculosis; receiving climatic and medical treatment; appetite impaired; occasionally diarrheal stools two or three times daily, which, however, soon subsided.

Diagnosis.—Pulmonary tuberculosis in the third stage; right tubercular pleurisy.

Present Illness.—Constitution poor; nourishment impaired; skin and mucous membrane anemic; cheeks flushed; larynx slightly congested; neck long; no lymphatic glands swollen; typical pigeon chest; right lung very weak in respiratory sounds; slight dullness of frontal side of the right lung down to the fourth intercostal space; râles at apex; bronchial respiration elsewhere; slight dullness over lateral side of the right lung; râles and friction sounds also heard; few râles on lateral side of left lung at intercostal space; normal precardial dullness; no tenderness or hard nodules in the bowels. Body temperature 38.1°C. Pulse over 101. Body weight 43.7 kilos. The bacilli in the sputum correspond to Gaffky's No. VI.

Progress.—The first injection of 16 mg. was given on Feb. 9, 1915. On Feb. 14 the temperature fell to 37.6°C., when the patient was discharged from the hospital. In the evening the temperature rose to 38.2°C. The third injection (16 mg.) and the fourth (14 mg.) were given on Mar. 9 and Apr. 27, respectively, but brought about gradual rise of temperature, more bacilli in the sputum, and extension of the lesions, as shown in the chart. Emaciation gradually set in, and the body weight fell to 38.2 kilos. The injection of the preparation was therefore suspended for the time being.

Case 10.—E. T., male, aged 34 years. Father died of an indefinite disease; mother healthy. Six brothers and sisters, one of whom died while young, also of an indefinite disease. No inherited tendency toward tuberculosis.

The patient had been healthy until he was about 14 years old, when he contracted pleurisy after a cold, and then tuberculosis. The symptoms were becoming worse. In 1914 he was operated on for hemorrhoids. Since then he has been suffering from an increase of cough, expectoration, and fever; at the same time night sweats and dyspnea appeared; could not walk because of emaciation. Appetite poor.

Diagnosis.—Pulmonary tuberculosis in the third stage, and hemorrhoids.

Present Illness.—Constitution robust; nourishment impaired; skin and mucous membrane very anemic; features agonal; larynx somewhat congested; neck long; no swollen lymphatic glands; thorax flat; on the left side breathing impaired; dullness down to the second rib on the frontal side of the right lung; on the same side slight dullness down to the costal margin; all the remainder dull; at the region

where slight dullness is elicited bronchial sounds are heard on auscultation; no respiratory sounds in the region of the dullness; slight dullness down to the fifth intercostal space on the frontal side of the left lung; at the second intercostal space tympanic sounds at some points; on the lateral side dullness over a region as wide as three fingers; bronchial respiratory sounds are heard over these regions; normal precardial dullness; no change in the heart sound. Von Pirquet reaction, +, +, +. The bacilli in the sputum correspond to Gaffky's No. III. Temperature 38.9°C. Pulse 108, weak. Weight 50.1 kilos.

Progress.—The first injection of 16 mg. was given on Jan. 19, 1915, the second (16 mg.) on Feb. 2. Temperature fell to 37.3–37.7°C. on Feb. 9. The third injection (16 mg.) was given on Feb. 16. By this time the general condition improved markedly. The fourth injection (17 mg.) was given on Mar. 2. The temperature rose to 38°C. and the bacilli in the sputum also increased to Gaffky's No. VII. The physical phenomena were intensified until an interval of 3 weeks had elapsed, when the temperature fell to 37.1°C. The fifth (16 mg.), the seventh (15 mg.), and the eighth injections (16 mg.) were given on Apr. 7 and 20, and May 4, respectively. At present the temperature is about 37°C. The physical phenomena are represented in the accompanying charts. Though improvement is obvious, the bacilli in the sputum have not disappeared.

Case 11.—N. T., male, aged 23 years. Father living; mother died of typhoid fever; seven paternal uncles and aunts, three of whom died of an indefinite disease; one is suffering from tuberculosis; all the rest are healthy; no brothers or sisters.

The patient has been weak since birth; contracted whooping cough in his 8th year; ever since has been unwell during the winter; contracted pneumonia once; has empyema of the maxillary sinus; contracted apical tuberculosis 3 years ago, which subsided after clinical treatment, but is not yet completely cured; rarely has pain in the thorax; appetite good; stools once daily.

Diagnosis.—Pulmonary tuberculosis in the first stage.

Present Illness.—Constitution and nourishment good; skin and mucous membrane not anemic; larynx slightly congested; neck long; no swelling of the jugular lymphatic glands; thorax symmetrical; breathing symmetrical; right apex slightly resistant at the supraclavicular fossa; precardial dullness reaches as far as the breasts; on auscultation no change is perceptible; bowels normal. Von Pirquet reaction, +, +, +. Weight 57.2 kilos. Temperature 37°C. Pulse 74, regular. No tubercle bacilli in the sputum.

Progress.—The first injection of 16 mg. was given on Dec. 11, 1914. Many râles appeared along the line bordering the right lung and the liver, as is shown in the chart; the apex showed slight dullness with a few râles; many râles were heard about the region corresponding to the heart; on the lateral side of the right lung slight dullness was produced over a region as wide as three fingers, where some râles were also heard. Tubercle bacilli in the sputum correspond to Gaffky's No. II. These phenomena completely disappeared in 7 days. The second injection (16 mg.), the third (16 mg.), and the fourth (16 mg.) were given

on Dec. 26, Jan. 8, and 22, respectively. No reaction was produced, and the results of the fifth injection (17 mg.) brought about some reaction. Since then four injections were made, but no reaction was produced. All examinations of the sputum have been negative. Von Pirquet negative. Treatment suspended.

SUMMARY.

A general review of the cases will, I think, indicate that the preparation[2] greatly improves or apparently cures pulmonary and surgical tuberculosis in the first and second stages, and that it seems also to produce beneficial effects upon the disease in the third stage. The duration of these beneficial effects is still to be established by more numerous trials and many years of observation.

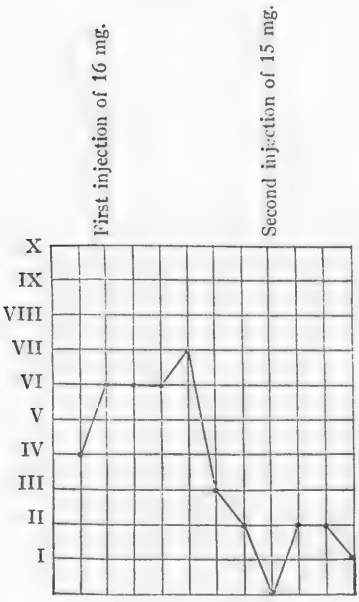
The preparation must be given intravenously, and the doses must be increased or decreased according to the age and constitution of each patient (page 156). Moreover, it should be borne in mind that the pathological phenomena and the constitution of each patient have much to do with the determination of the dose. The manner of action of the preparation is not yet entirely clear. But if it acts primarily upon the tissues which bear the tubercular lesions and then indirectly against the germ, as I assume at present, the activity which the tissues exert will have much to do with the efficacy of the preparation. If this hypothesis is correct, the minimum doses (10 to 12 mg.) will be best suited to a patient who is greatly emaciated, and should be gradually increased as the reactions, pathological processes, nutrition, etc., indicate. In any case, the dose of the preparation must be determined by the condition and constitution of the patient. In animal experiments I have been fortunate enough to obtain results which no other preparation has given. The clinical application and the establishment of its full efficacy in human cases must be left to the physician.

I wish to express my indebtedness to Drs. Kitasato, Shiga, and Kusama, and also to Dr. Kanai and other members of the Kitasato Institute.

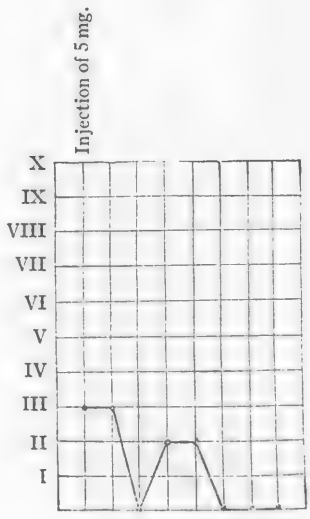
[2] The preparation has since been named "cyanocuprol."

The Roman numerals in Text-figs. 1 to 6 refer to the numbers in Gaffky's table:

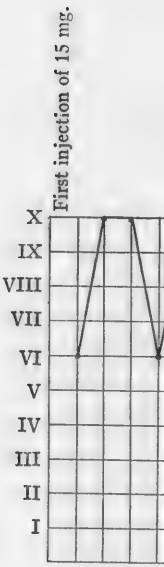
I.	Only 1 to	4	bacilli	in	whole	preparation.	
II.	Only	1	on an	average	in	many	fields.
III.	Only	1	"	"	"	"	each field.
IV.	2 to	3	"	"	"	"	" "
V.	4 to	6	"	"	"	"	" "
VI.	7 to	12	"	"	"	"	" "
VII.	13 to	25	"	"	"	"	" "
VIII.	About	50	"	"	"	"	" "
IX.	About	100	"	"	"	"	" "
X.	Over 100 in each field.						



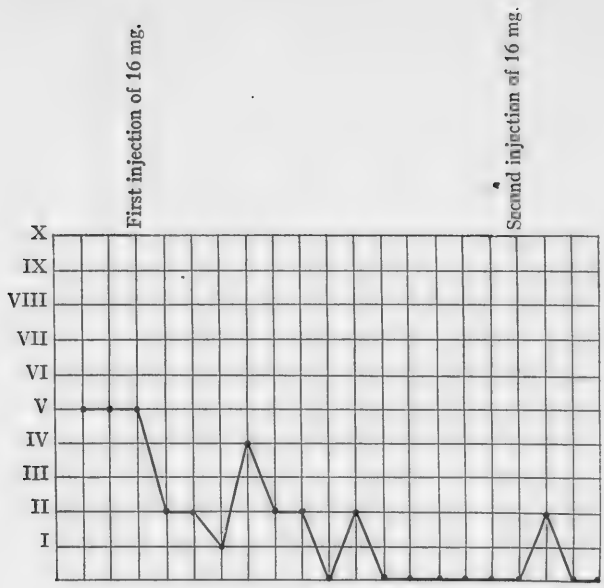
TEXT-FIG. 1. Case 2, male. The sputum is free from bacilli at present.



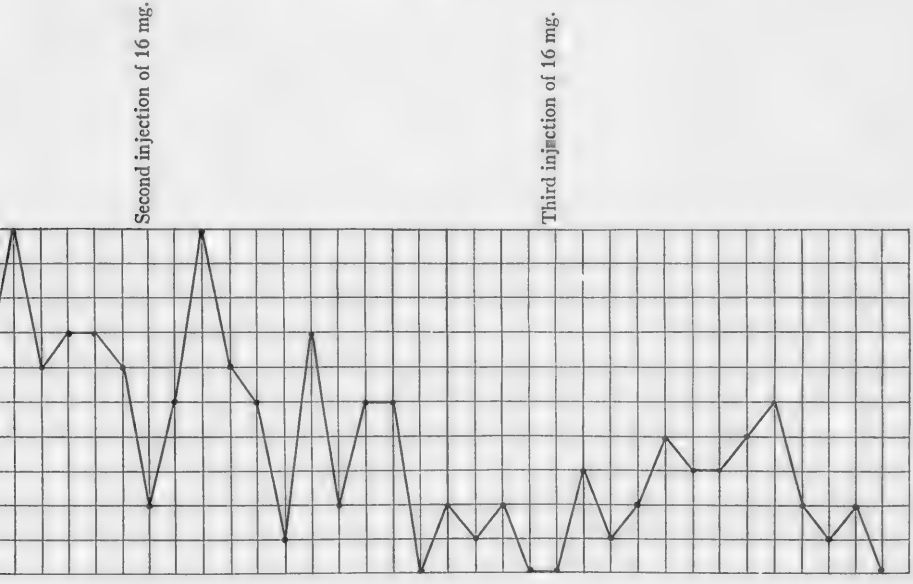
TEXT-FIG. 2. Case 3, male. The patient did not report again and therefore received no further treatment.



TEXT-FIG



TEXT-FIG. 3. Case 5, male. The sputum was examined under the microscope; negative results were obtained each time.

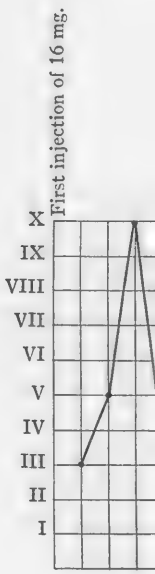


4. Case 8, male. Every microscopic examination has been negative for more than 4 months.

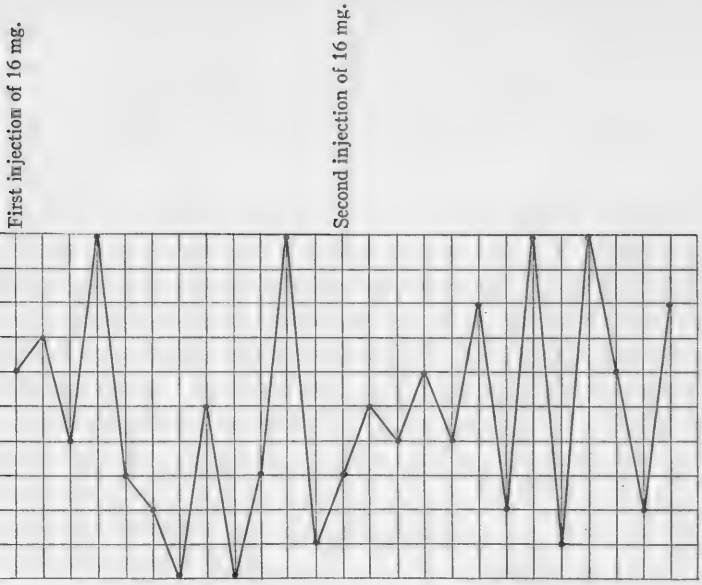
X
IX
VIII
VII
VI

IV
III
II
I

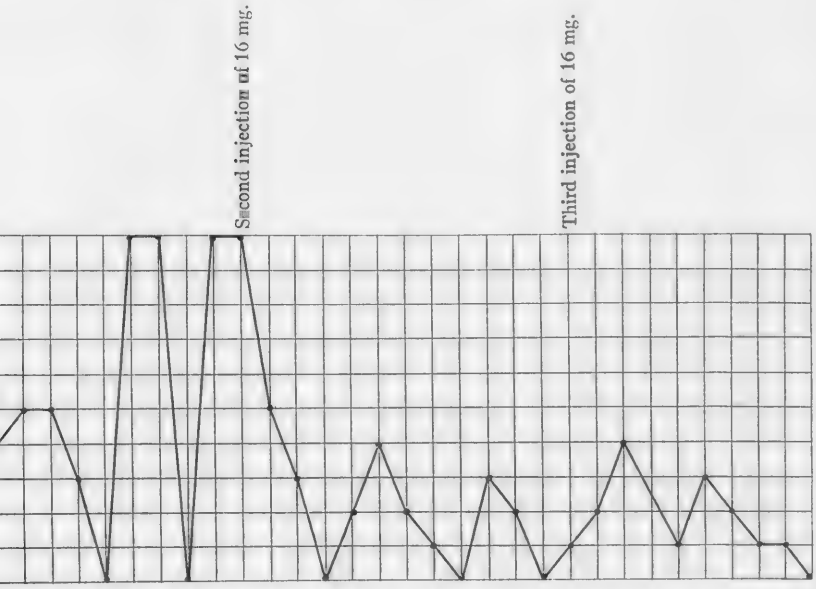
T
of b



TEXT-FIG.

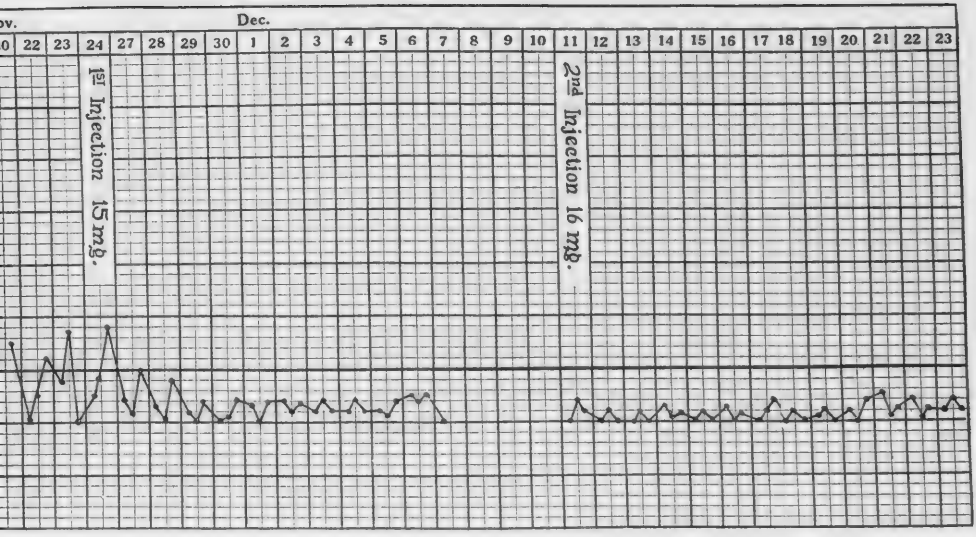


xt-Fig. 5. Case 9, female. The symptoms became worse and the number cilli in the sputum increased.

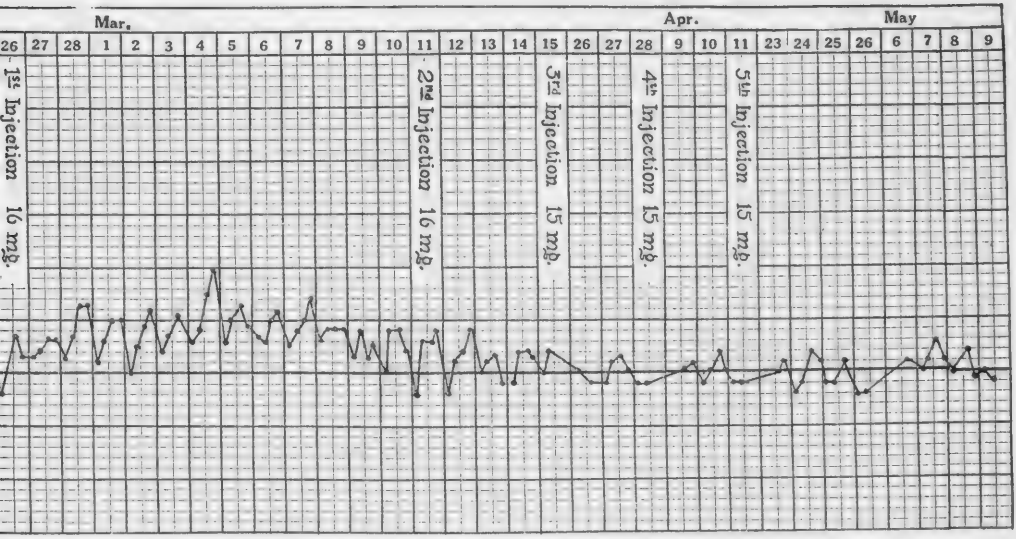


6. Case 10, male. After 4 months' treatment the sputum was free from bacilli.

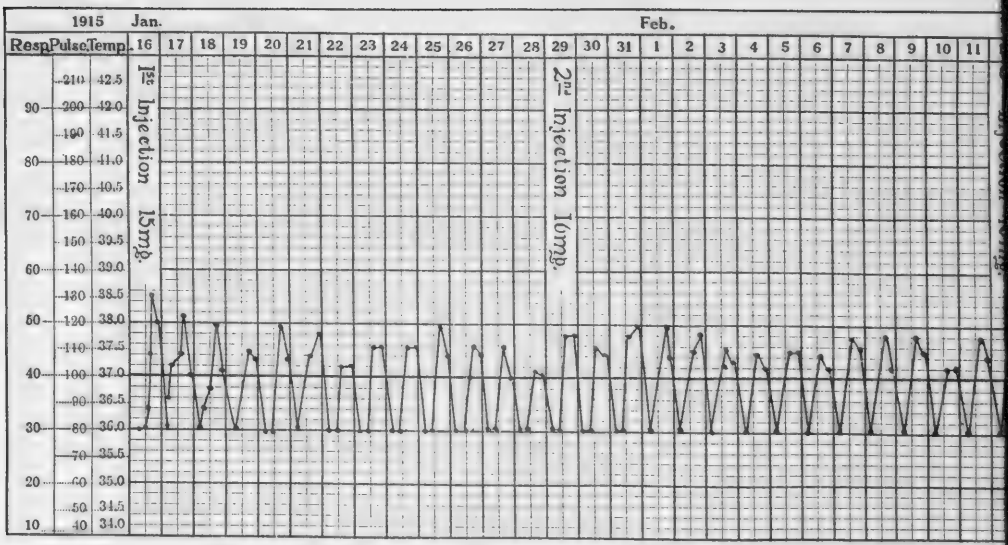
1914
Resp.Pulse.Temp
210 42.5
90 200 42.0
190 41.5
80 180 41.0
170 40.5
70 160 40.0
150 39.5
60 140 39.0
130 38.5
50 120 38.0
110 37.5
40 100 37.0
90 36.5
30 80 36.0
70 35.5
20 60 35.0
50 34.5
10 40 34.0
1915 Feb
Resp.Pulse.Temp. 25
210 42.5
90 200 42.0
190 41.5
80 180 41.0
170 40.5
70 160 40.0
150 39.5
60 140 39.0
130 38.5
50 120 38.0
110 37.5
40 100 37.0
90 36.5
30 80 36.0
70 35.5
20 60 35.0
50 34.5
10 40 34.0



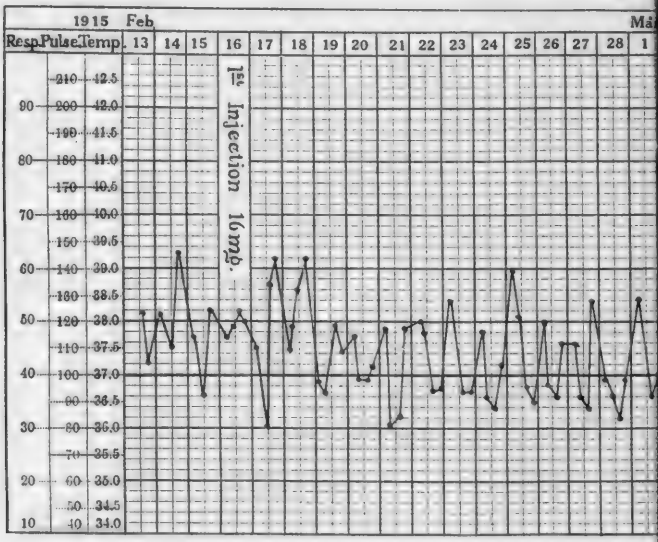
TEXT-FIG. 7. Temperature curve. Case 1, female.



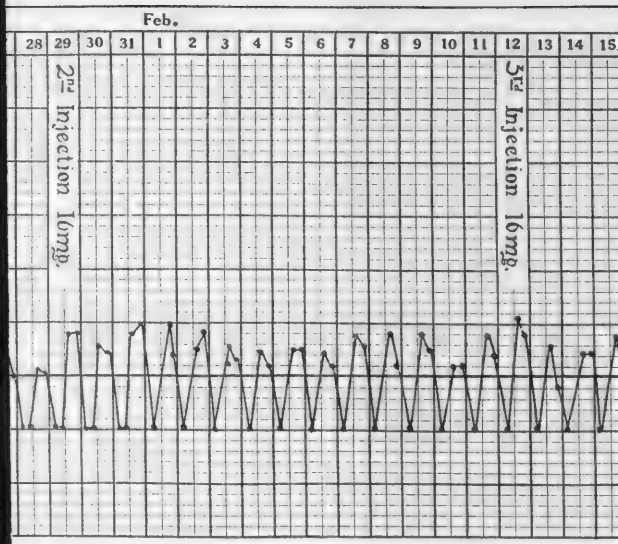
TEXT-FIG. 8. Temperature curve. Case 3, male.



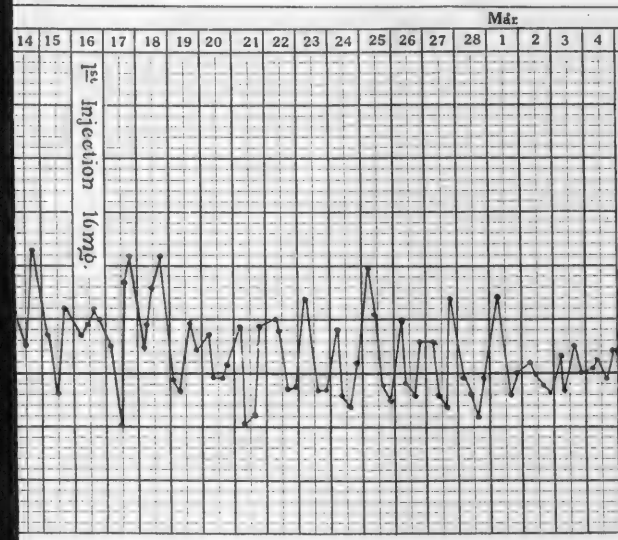
TEXT-FIG. 9. Temperature curve. Case



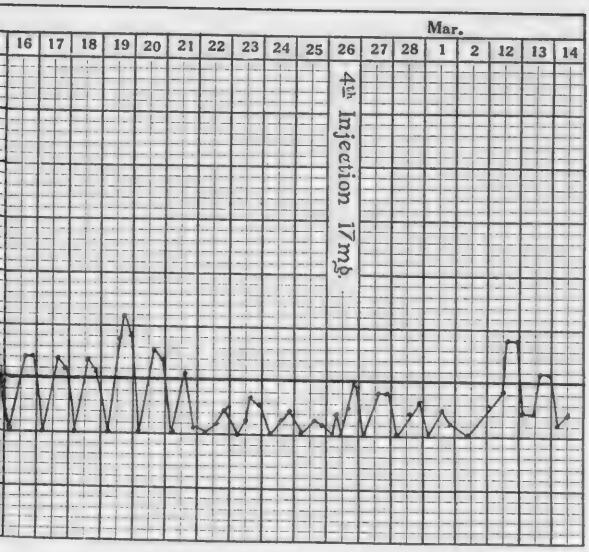
TEXT-FIG. 10. Temperature curve. Case

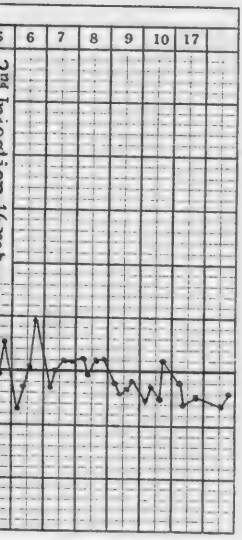


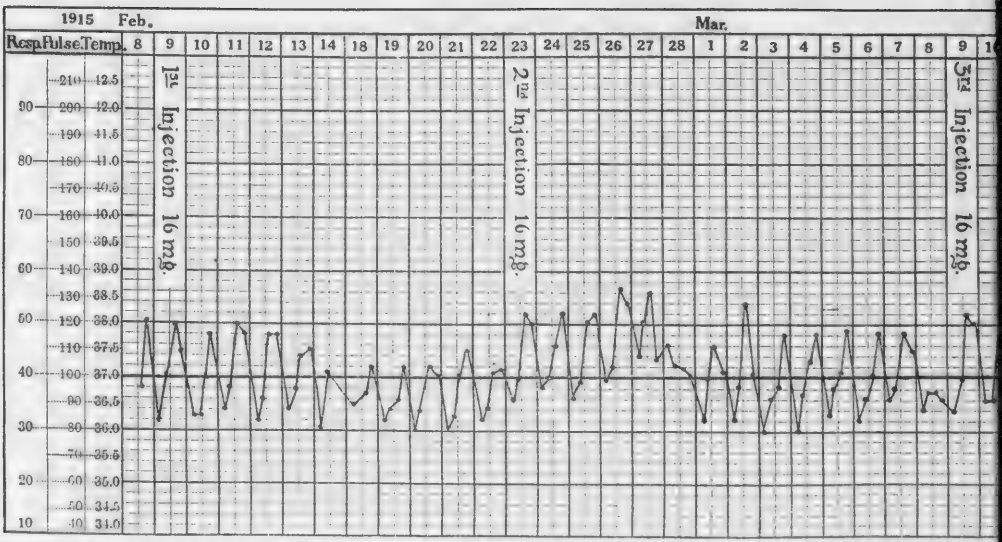
TEXT-FIG. 9. Temperature curve. Case 8, male.



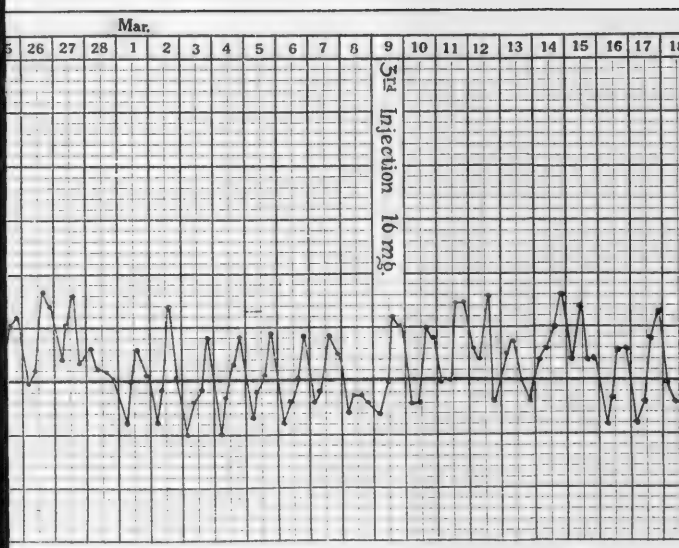
TEXT-FIG. 10. Temperature curve. Case 4, female.


Mar.
16 17 18 19 20 21 22 23 24 25 26 27 28 1 2 12 13 14
4th Injection 17mg.

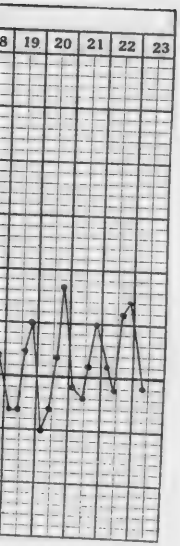

6 7 8 9 10 17
2nd Injection 16mg.

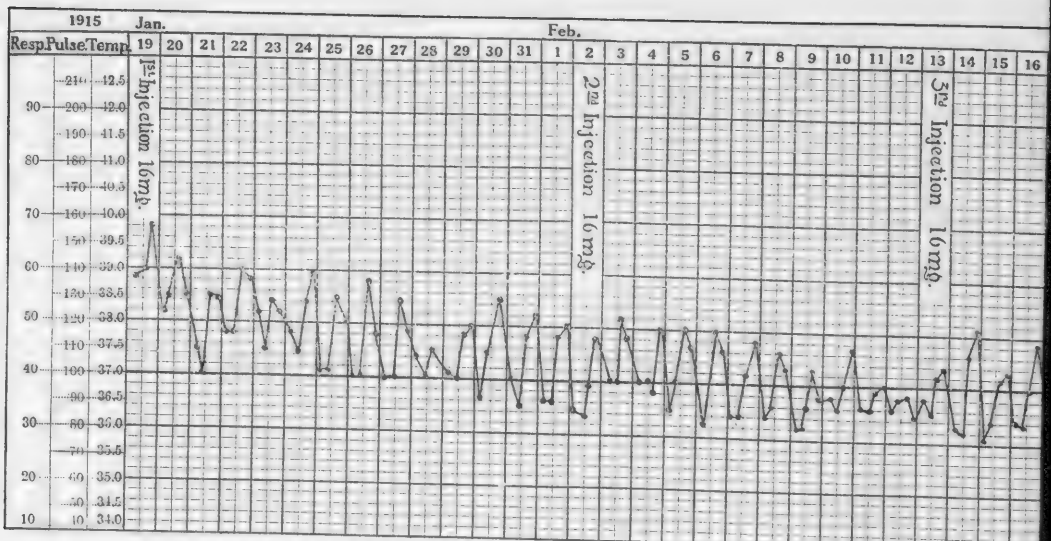


TEXT-FIG. 11. Temperature curve. Case 9, female.

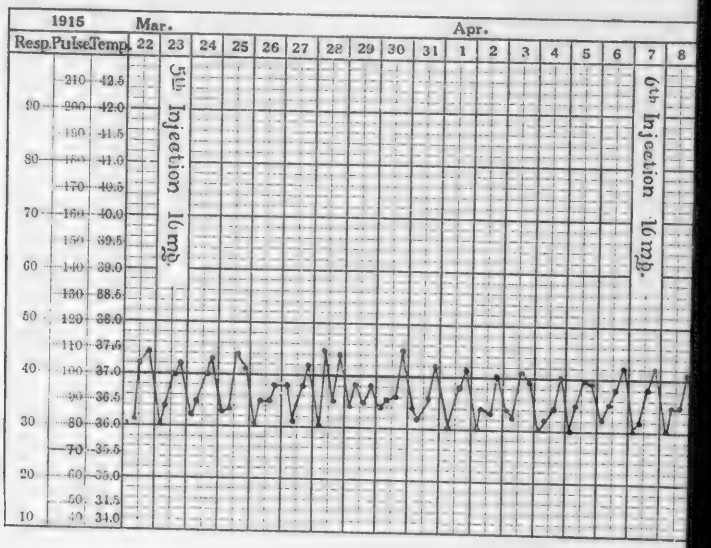


1. Temperature curve. Case 9, female.

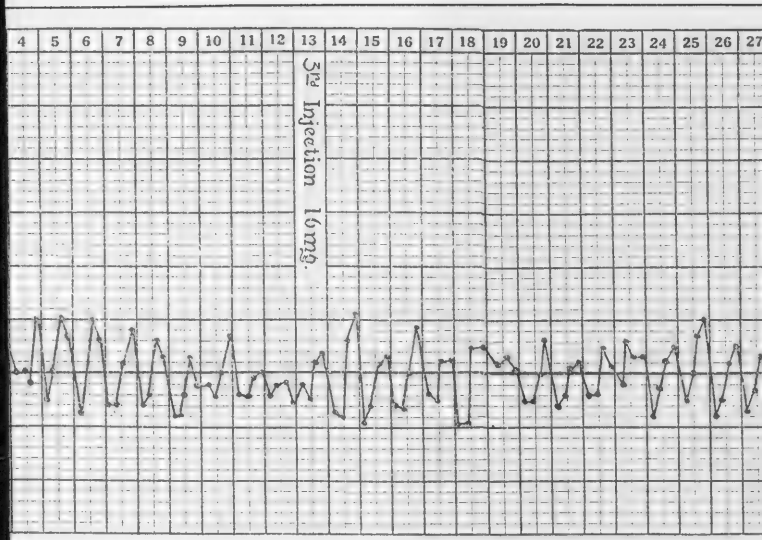

8
19
20
21
22
23



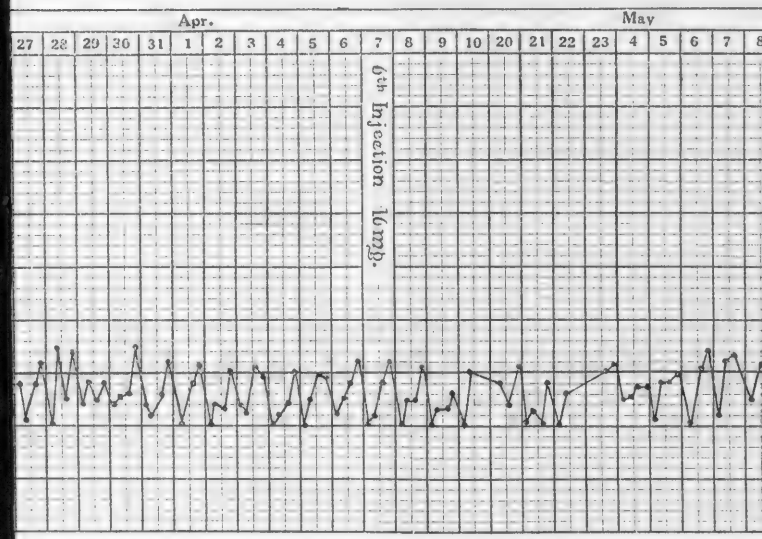
TEXT-FIG. 12. Tempera



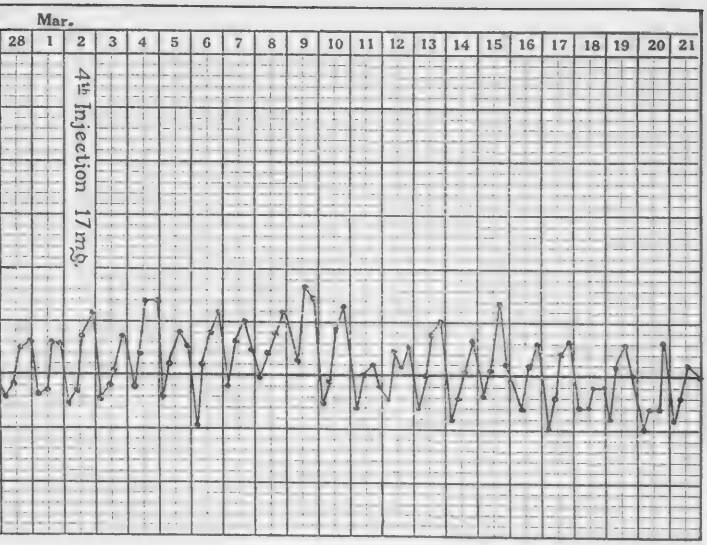
TEXT-FIG. 13. Temperatu

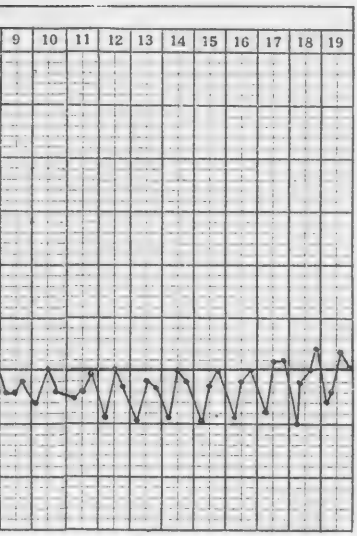


TEXT-FIG. 12. Temperature curve. Case 10, male.



TEXT-FIG. 13. Temperature curve. Case 10 continued.


Mar.
28 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21
4th Injection 17 mg.


9 10 11 12 13 14 15 16 17 18 19

Bronchial respiration sound.

Weak " "

Loss of " "

Rough " "

Interrupted " "

Long " "

Coarse râles.

Fine "

Consonant râles.

Vesicular "

Friction "

P Sibilant "

G Crackling "

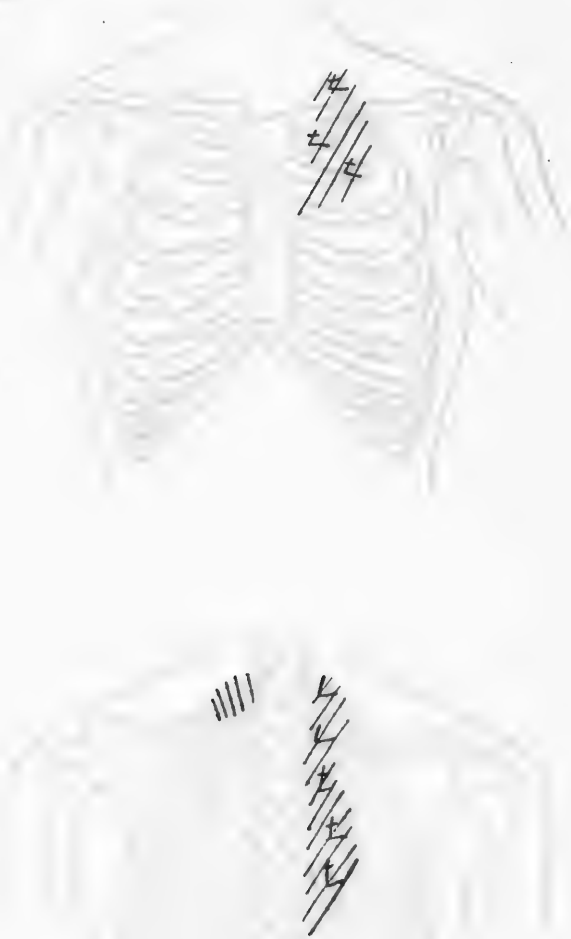
S Sonorous "

Short sound.

Dull "

Metallic "

Heart "



TEXT-FIG. 14. Case 6, male. Nov. 11, 1914.

Bronchial respiration sound.

Weak " "

Loss of " "

Rough " "

Interrupted " "

Long " "

Coarse râles.

Fine "

Consonant râles.

Vesicular "

Friction "

Sibilant "

Crackling "

Sonorous "

Short sound.

Dull "

Metallic "

Heart "

TEXT-FIG. 15. Case 6, male. Nov. 26, 1914.

Bronchial respiration sound.

Weak " "

Loss of " "

Rough " "

Interrupted " "

Long " "

Coarse râles.

Fine "

Consonant râles.

Vesicular "

Friction "

Sibilant "

Crackling "

Sonorous "

Short sound.

Dull "

TEXT-FIG. 16. Case 6, male. Dec. 8, 1914.

Metallic "

Heart "

Bronchial respiration sound.

Weak " "

Loss of " "

Rough " "

Interrupted " "

Long " "

Coarse râles.

Fine "

Consonant râles.

Vesicular "

Friction "

P Sibilant "

G Crackling "

S Sonorous "

Short sound.

Dull "

ty Metallic "

Heart "

TEXT-FIG. 17. Case 6, male. Jan. 12, 1915, no symptoms.

Bronchial respiration sound.

Weak " "

Loss of " "

Rough " "

Interrupted " "

Long " "

Coarse râles.

Fine "

Consonant râles.

Vesicular "

Friction "

P Sibilant "

G Crackling "

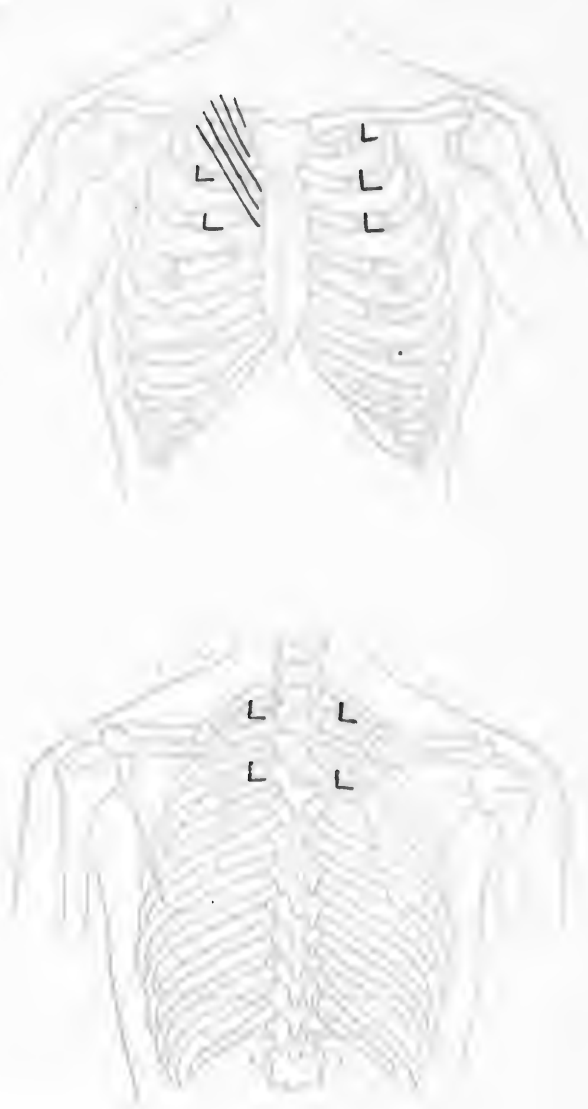
S Sonorous "

Short sound.

Dull "

ty Metallic "

Heart "



TEXT-FIG. 18. Case 7, male. Feb. 16, 1915.

Bronchial respiration sound.

Weak " "

Loss of " "

Rough " "

Interrupted " "

Long " "

Coarse râles.

Fine "

Consonant râles.

Vesicular "

Friction "

P Sibilant "

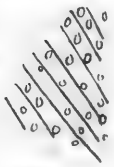
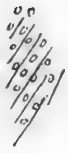
G Crackling "

S Sonorous "

Short sound.

Dull "

ty Metallic "

Heart "

TEXT-FIG. 19. Case 7, male. Feb. 20, 1915.

Bronchial respiration sound.

Weak " "

Loss of " "

Rough " "

Interrupted " "

Long " "

Coarse râles.

Fine "

Consonant râles.

Vesicular "

Friction "

Sibilant "

Crackling "

Sonorous "

Short sound.

Dull "

Metallic "

Heart "

TEXT-FIG. 20. Case 7, male. Feb. 26, 1915.

L Bronchial respiration sound.

t Weak " "

t Loss of " "

Rough " "

Interrupted " "

L Long " "

Coarse râles.

Fine "

Consonant râles.

Vesicular "

Friction "

P Sibilant "

G Crackling "

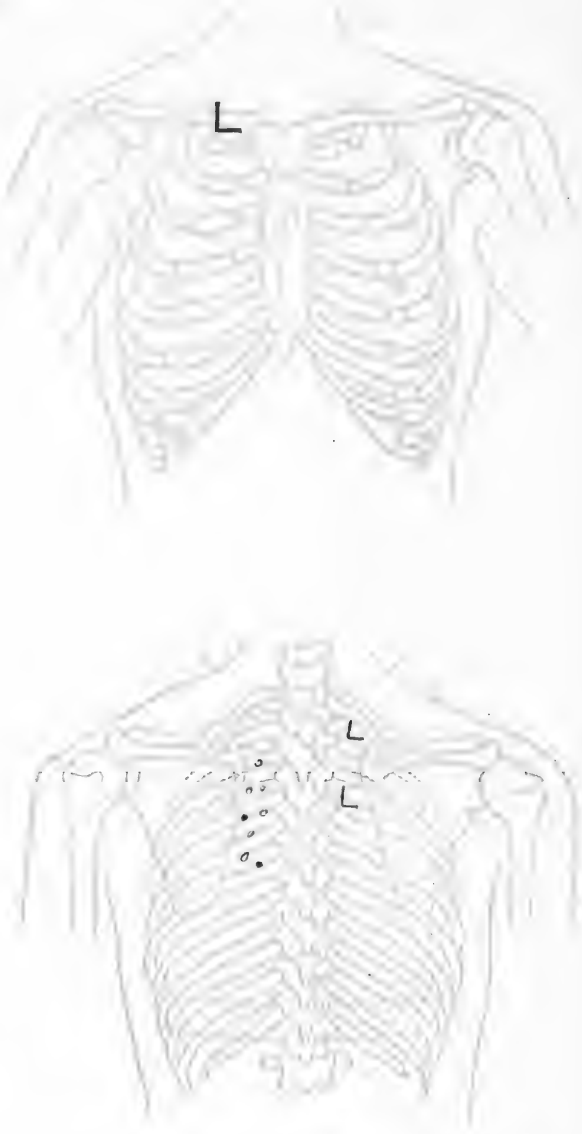
S Sonorous "

Short sound.

Dull "

ty Metallic "

J Heart "



TEXT-FIG. 21. Case 7, male. May 7, 1915. Note the appearance of râles in the intrascapular region, after an interval of 3 months during which time he did not receive the injection.

Bronchial respiration sound.

Weak " "

Loss of " "

Rough " "

Interrupted " "

Long " "

Coarse râles.

Fine "

Consonant râles.

Vesicular "

Friction "

Sibilant "

Crackling "

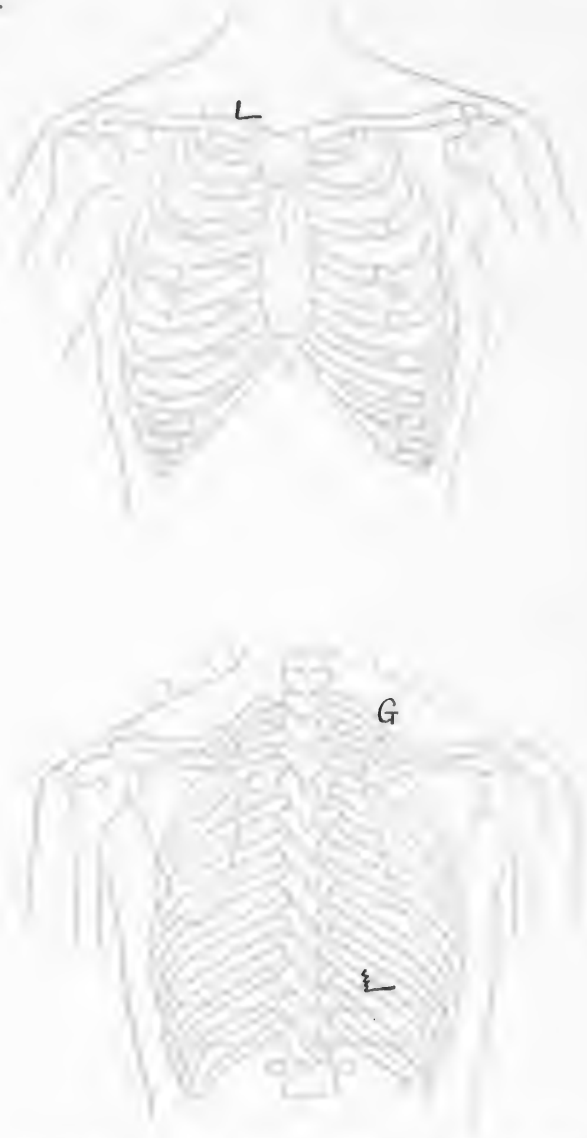
Sonorous "

Short sound.

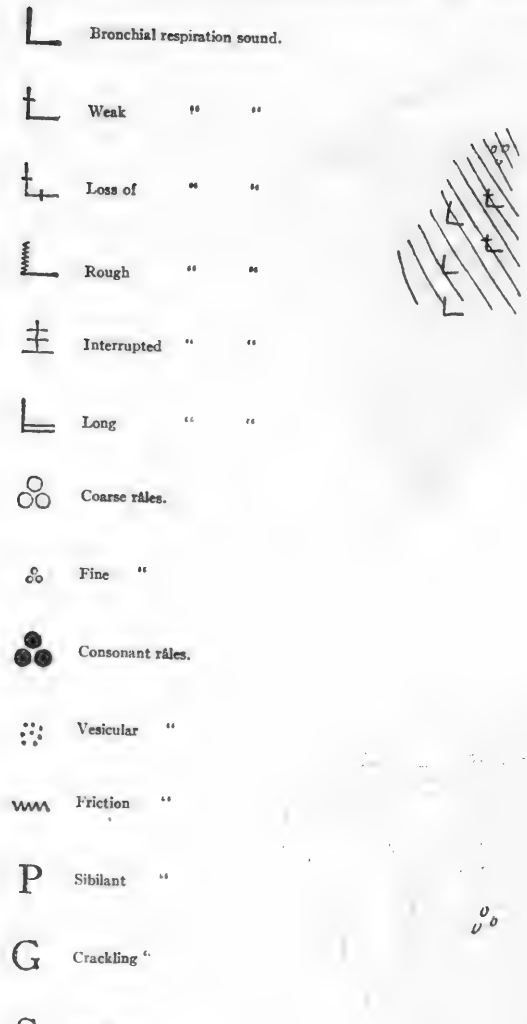
Dull "

Metallic "

Heart "



TEXT-FIG. 22. Case 7, male. May 20, 1915. The râles disappeared after one injection of 15 mg. and the injection was discontinued.



TEXT-FIG. 23. Case 9, female. Feb. 8, 1915.

Bronchial respiration sound.

Weak " "

Loss of " "

Rough " "

Interrupted " "

Long " "

Coarse râles.

Fine "

Consonant râles.

Vesicular "

Friction "

P Sibilant "

G Crackling "

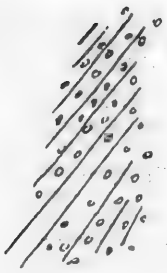
S Sonorous "

Short sound.

Dull "

ty Metallic "

Heart "



TEXT-FIG. 24. Case 9, female. Apr. 19, 1915.

Bronchial respiration sound.

Weak " "

Loss of " "

Rough " "

Interrupted " "

Long " "

Coarse râles

Fine "

Consonant râles.

Vesicular "

Friction "

P Sibilant "

G Crackling "

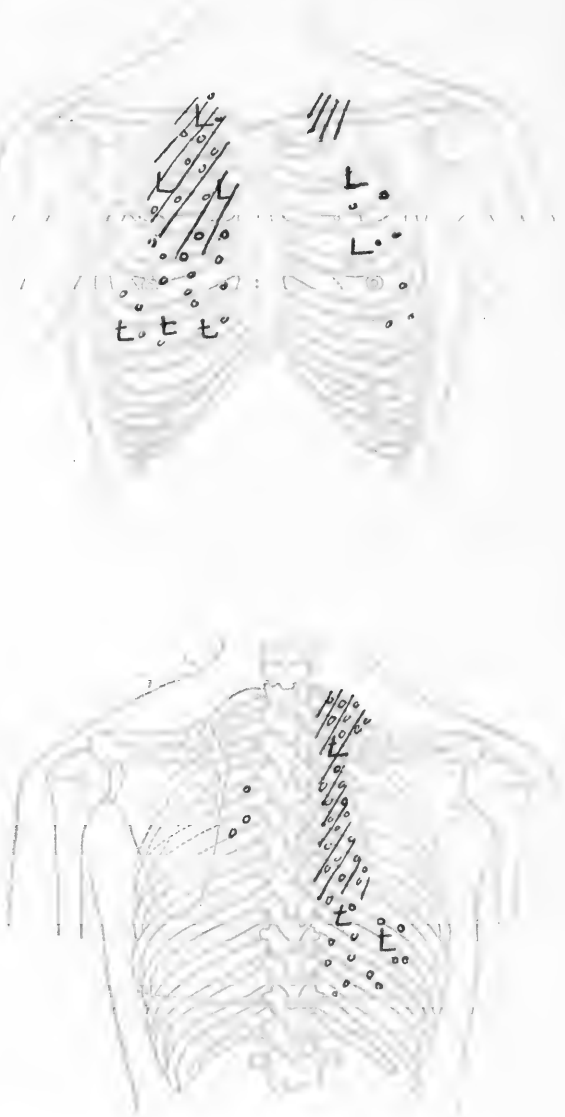
S Sonorous "

Short sound.

Dull "

Metallic "

Heart "



TEXT-FIG. 25. Case 9, female. Apr. 27, 1915.

Bronchial respiration sound.

Weak " "

Loss of " "

Rough " "

Interrupted " "

Long " "

Coarse râles.

Fine "

Consonant râles.

Vesicular "

Friction "

Sibilant "

Crackling "

Sonorous "

Short sound.

Dull "

Metallic "

Heart "

TEXT-FIG. 26. Case 10, male. Jan. 19, 1915.

Bronchial respiration sound.

Weak " "

Loss of " "

Rough " "

Interrupted " "

Long " "

Coarse râles.

Fine "

Consonant râles.

Vesicular "

Friction "

Sibilant "

Crackling "

Sonorous "

Short sound.

Dull "

Metallic "

Heart "

TEXT-FIG. 27. Case 10, male. Feb. 13, 1915.

Bronchial respiration sound.

Weak " "

Loss of " "

Rough " "

Interrupted " "

Long " "

Coarse râles.

Fine "

Consonant râles.

Vesicular "

Friction "

P Sibilant "

G Crackling "

S Sonorous "

Short sound.

Dull "

ty Metallic "

Heart "

TEXT-FIG. 28. Case 10, male. Apr. 20, 1915.

Bronchial respiration sound.

Weak " "

Loss of " "

Rough " "

Interrupted " "

Long " "

Coarse râles.

Fine "

Consonant râles.

Vesicular "

Friction "

Sibilant "

Crackling "

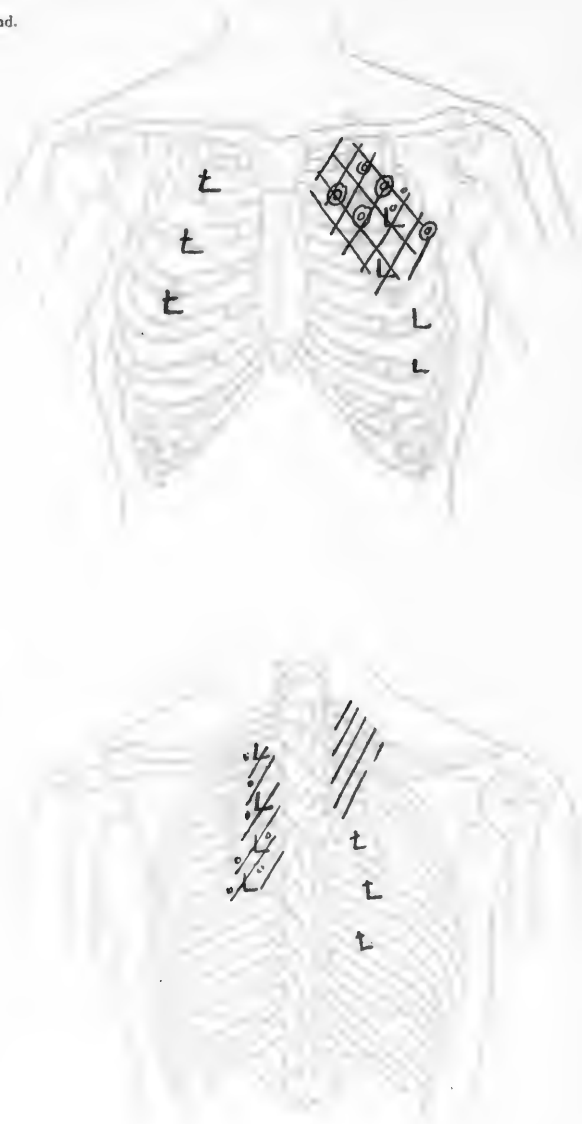
Sonorous "

Short sound.

Dull "

Metallic "

Heart "



TEXT-FIG. 29. Case 10, male. May 17, 1915.

Bronchial respiration sound.

Weak " "

Loss of " "

Rough " "

Interrupted " "

Long " "

Coarse râles.

Fine "

Consonant râler.

Vesicular "

Friction "

P Sibilant "

G Crackling "

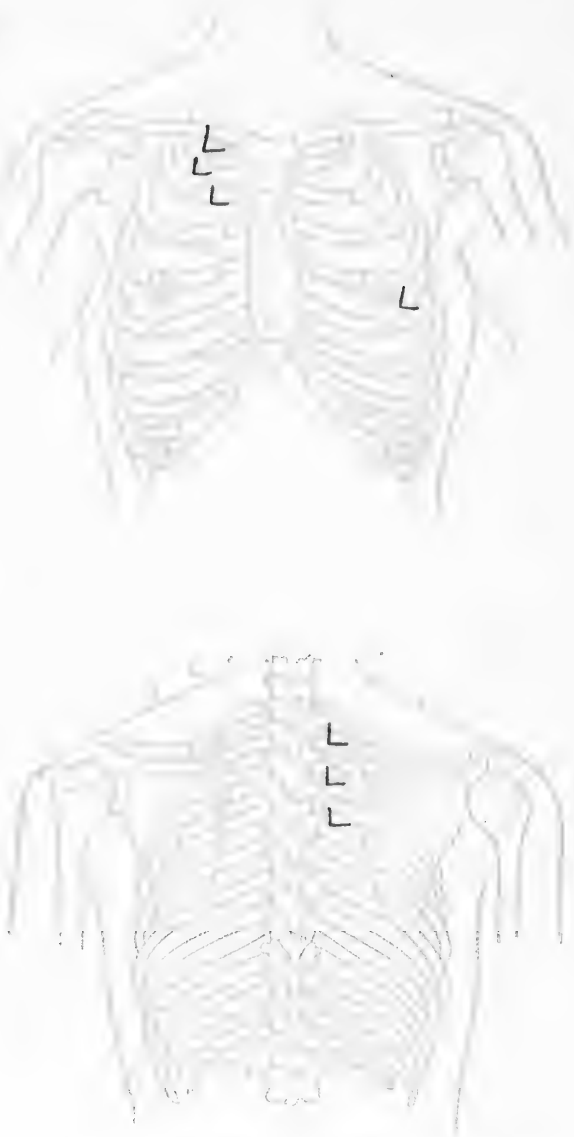
S Sonorous "

Short sound.

Dull "

Metallic "

Heart "



TEXT-FIG. 30. Case 11, male. Dec. 3, 1915.

L Bronchial respiration sound.

t Weak " "

t Loss of " "

Rough " "

Interrupted " "

Long " "

Coarse râles.

Fine "

Consonant râles.

Vesicular "

Friction "

P Sibilant "

G Crackling "

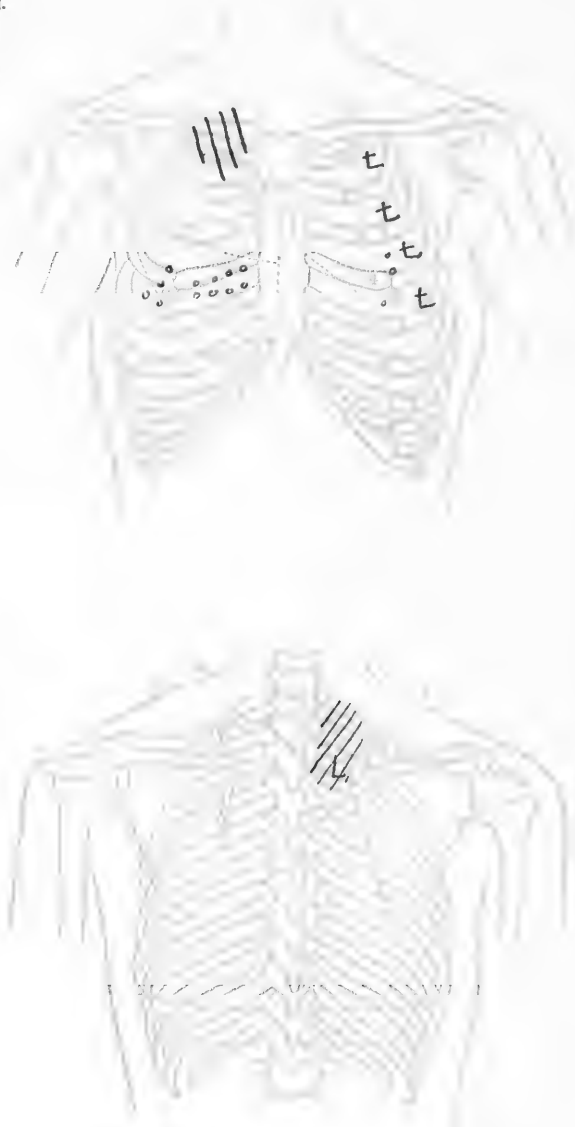
S Sonorous "

Short sound.

Dull "

ty Metallic "

Heart "



TEXT-FIG. 31. Case 11, male. Dec. 11, 1915.

THE TREATMENT OF TUBERCULOSIS WITH CYANOCUPROL.

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(Received for publication, February 7, 1916.)

The present paper deals with the clinical treatment of tuberculous patients with cyanocuprol. I believe it desirable to report the work as far as it has progressed, although the cases are still too few to permit conclusions regarding the efficacy of the preparation. A later communication covering this point may be expected.

General Considerations.

Koga[1] reported that the intravenous injection of cyanocuprol brings about a degree of reaction in tuberculous cases, which is proportional to the amount given in each instance. However, the relation between the reaction and the efficacy has not yet been definitely established. Too great a reaction produced severe effects on the patient and smaller doses have therefore been given. The reactions have thus been eliminated, but the results seem incidentally to have become inferior to those obtained by Koga with the larger doses. The tubercle bacilli in the sputum, also, did not show such a marked decrease as under the influence of larger doses.

Although cyanocuprol produces favorable results in the condition taken as a whole when administered in adequate doses, yet indifferent cases sometimes occur in which its efficacy is doubtful. This indifferent result may depend upon insufficient dosage. Moreover, the constitution of the patient and the nature of the pathological processes play an important part in determining the effects.

Indications and Contraindications.—Cases suitable for the application of cyanocuprol are far more numerous than for the tuberculin

[1] Koga, G., *J. Exp. Med.*, 1916, xxiv, 149.

treatment, since it may be administered in almost all instances of tuberculosis. Even in the final stages the preparation may be given without danger, although with little hope of improvement. Patients suffering from progressive tuberculosis in the third stage sometimes gave an unexpectedly good result, and high fever abated after an intravenous administration. Pulmonary hemorrhages sometimes occurred during the reaction period, but they were traced invariably to carelessness on the part of the patient. The data at hand suffice to state that the preparation does not influence injuriously pulmonary hemorrhages but rather increases the coagulability of the blood so that the hemorrhage may be arrested. Cases with fever in consequence of cold may be given the drug without inconvenience. However, it may be advisable to wait until recovery from the cold takes place before giving the drug. The drug may be given to tuberculous patients with chronic diseases of the heart and kidney, and glycosuria and beri-beri, but it must not be given to patients having irregular or accelerated pulse (*e.g.*, over 120) or weak tonus of the pulse. The preparation may be given during menstruation and pregnancy provided care be exercised to avoid any unusual reaction.

Dosage.—There exists an intimate relation between the proper dose and the condition of the patient, for upon the dose seems to depend largely whether or not improvement follows. We are now studying this point with the utmost care. It seems to be much more difficult to ascertain the proper dose of cyanocuprol for each individual than of tuberculin. For instance, in some cases a reaction set in in consequence of an increase of the dose by 0.25 cc., in others a rise of temperature occurred even when the same dose was given each time. The dose of tuberculin may be settled comparatively easily by the degree of von Pirquet reaction or the reaction produced by the intracutaneous injection of tuberculin. But with cyanocuprol we have as yet no preparatory test by which the dose can be determined. We are at present determining, according to our past experiences, the amount for each individual case by the following standard doses, which have been chosen with reference to the site and severity of the pathological processes.

TABLE I.

Type of disease.			Dose. cc.
Pulmonary tuberculosis,		1st stage	7.0–7.5
"	"	2nd "	6.0–7.0
"	"	3rd "	4.0–6.0
Laryngeal	"		4.0–6.0
Intestinal	"		4.0–6.0
Pleural	"		4.0–6.0
Peritoneal	"		4.0–6.0
Kidney	"		3.0–5.0
Bone	"		7.0–8.5
Joint	"		7.0–8.5
Cutaneous	"		7.0–8.5
Glandular	"		7.0–8.5

Table I gives the standard dose for adult men, and must be altered according to the general condition of the patient. For instance, patients having high fever, showing a tendency to pulmonary hemorrhage, suffering from neurasthenia, malnutrition, extreme anemia, or showing marked progress of the pathological processes, heart disease, or chronic diseases other than tuberculosis, or presenting a wide tuberculous lesion, etc., should receive smaller doses. The body weight would naturally seem to influence the dose, but my experience has led me to the conclusion that there is no need to vary the dose in proportion to the body weight. However, it must be decreased according to the patient's age; *e.g.*, a boy 10 years old should receive half the dose given to an adult man. The dose for the second injection should be made according to the degree of the reactions produced by the first, as well as by the general condition of the patient at the time of the injection. By a proper dose is meant the amount of the preparation which produces no or only a slight reaction, which disappears 2 or 3 days after the injection, and shows some improvement within 2 weeks. If these results are achieved, the dose should not be altered but should be continued for several injections until a change is deemed desirable. If too great a reaction, *i.e.*, fever exceeding 1°C., is produced, or if a local reaction lasting more than 3 days should occur, the dose must be decreased. If, on the contrary, neither reaction nor improvement is observed, the dose is increased by 0.25 cc. at the next injection. In

severe cases or cases suffering from progressive lesions, the increase must be made with special care.

Interval between Injections.—Great care should be exercised to allow a sufficient interval between the injections, as the interval as well as the dose seems to have much to do in bringing about improvement. The doses shown in Table I are the amounts that should be given once every other week. The injection should never be given with a shorter interval than a fortnight, as otherwise an unfavorable turn in the general symptoms may follow. Takano[2] reports that he gave lepers large doses weekly or sometimes twice a week, and observed no ill effects. But with tuberculosis such an attempt should not be made. Our experience has convinced us that Koga's view, based on animal experiments, of allowing an interval of 2 weeks between injections is correct. Prolongation of the interval may be made without harmful effects. If, therefore, the reaction produced by the injection should last more than 1 week, the succeeding injection must be postponed.

Reactions and Effects.—Koga has observed that the administration of cyanocuprol may be accompanied by striking reactions. But by diminishing the dose no reaction will be produced, and even if it should appear, no serious symptoms will develop. As a rule, the fever does not rise above 1°C., and the reactions disappear in 2 or 3 days, rarely lasting more than 1 week. The fever is sometimes preceded by a slight chill. Fever does not necessarily accompany the pain in the joints. The general reactions are headache, dullness in the limbs, lack of appetite, etc., and are so slight that no special treatment is called for. A fleeting inflammation appears in the lesion, as pointed out by Koga, but by the improved method of treatment, regional inflammation is avoided. The pulmonary dullness is rarely increased, and if increased it is slight. Râles are often heard, but they disappear in 2 or 3 days with no other treatment than confinement in bed. During the period of reaction the cough and sputum often increase, and if care is not taken to restrain them, hemoptysis may occur. Only one case out of more than 100 cases that I treated suffered from severe pulmonary hemorrhage.

[2] Takano, R., *J. Exp. Med.*, 1916, xxiv, 207.

Case Reports.

Case 1.—Male; age 43 years. Average build. Family history negative. Infiltration of the upper lobe of the right lung. Pulmonary hemorrhage occurred in July, 1914. A diagnosis of apical tuberculosis was made. The patient has complained of coughing and sputum since Feb., 1915. Temperature 37.5°C. Pulmonary hemorrhage of about 200 cc. took place 2 weeks before admission. Nutrition fair. Anemic. Apex of the right lung dull; medium râles were heard in the same region. 7.5 cc. of cyanocuprol were given at the first injection, and in the evening a pulmonary hemorrhage of about 50 cc. occurred. For 10 days the patient expectorated bloody sputum. After an interval of 2 weeks a second injection of 7.5 cc. was given. This time he presented no ill effects, and rarely expectorated bloody sputum. After five injections he returned to his home. At that time the regional dullness had diminished, and the râles had disappeared. The bacilli in the sputum, which before treatment had been equal to Gaffky's No. VIII, were reduced to No. IV or No. V. The sputum decreased considerably. The patient gained 3.6 kilos in weight.

In one case a severe reaction occurred which resulted in an aggravation of the general symptoms.

Case 2.—Female; age 21 years. Average build. Family history positive. Suffered from infiltration of the left upper lobe of the lung. Right apical tuberculosis. Has always been healthy; no serious illness. The patient suffered from bronchial catarrh, which soon subsided and left no subjective symptoms. Nutrition fair. Face pale. Temperature normal. Pulse more than 90. On the back a dull sound was heard from the apex down to the second intercostal space covering the upper half of the left side of the interscapular region. The right side of the interscapular region had also a slight dull sound. At the left apex a number of consonant râles were heard, and at the right apex a few small râles. 7.5 cc. of cyanocuprol were given at the first injection. On the day of the injection the body temperature rose to 38.1°C. The next evening it remained at 38.4°C., and fell on the 3rd day to 37.4°C. The patient left the hospital against the advice of the physicians in charge. She reported that she had had a temperature of 37.9°C., which became normal in about 2 weeks. No change was observed in the râles and dull sound, but she complained of the sputum which did not occur before the injection. Blood streaks were observed several times in the sputum. The second injection of 7 cc. was made in 2 weeks. This time the dull sound and râles increased slightly, and on the following day the temperature rose as high as 39°C. It was preceded by shivering but no chill. The patient was dismissed on the 3rd day after the injection Every evening the temperature rose to 38.3–38.4°C., and in about a week pneumonic symptoms developed. The temperature rose as high as 39.4°C. The dull sound and the râles appeared over the whole region of the left lung. These symptoms prevented my attempting further

treatment with cyanocuprol. The patient suffered from extreme emaciation and died in about 3 months.

In this case failure resulted partly from oversensitiveness to the preparation, but chiefly from the refusal of the patient to remain quiet during the period of pronounced reaction, and also to lack of the necessary interval between the injections.

In one case severe pain was caused by the injection.

Case 3.—Male; age 43 years. Average build. Family history negative. The patient was suffering from infiltration of the right upper lobe and left apex, together with laryngeal and intestinal (?) tuberculosis. Has always been healthy; no serious illness. Since Jan., 1915, he has complained of harshness of the voice, with pain in the throat; not conscious of fever. For the past several days he has been suffering from diarrhea,—four or five stools a day,—coughing, and sputum. Appetite poor. Nutrition poor. Severe anemia. Temperature 38°C. Pulse 90. Dull sound over the region of the right apex down to the second intercostal space in front and the lower corner of scapula on the back, from the left apex to the supraclavicular fossa in front and over the corresponding region of the back. Large and small râles heard over this entire region. General respiration sound weak. The bowels are sunken. In the right iliac cavity a hard mass as large as a pigeon's egg is felt, which is not tender. Von Pirquet reaction slightly positive. After the first injection of 6 cc. of cyanocuprol the temperature reached 38.8°C. No change was observed in the lungs and intestines. The pain in the throat subsided for a short time, but reappeared on the 5th day. This time the pain was more severe, and difficulty in swallowing developed. In consequence of severe emaciation the treatment was suspended.

Koga[1] reports a case of intestinal tuberculosis that developed symptoms resembling dysentery in consequence of the injection of cyanocuprol. I have had a similar case.

Case 4.—Female; age 34 years. Average build. Mother died of pleurisy. The patient has the progressive form of pulmonary tuberculosis. Had been healthy until she contracted pneumonia in 1913. In 1914 had pleurisy of the left side, and in Mar., 1915, serous pleurisy of the right side. She catches cold easily, and has complained of harshness of the voice since Mar., 1915, with large quantities of sputum. No diarrhea. Nutrition poor. Face pale, presenting an appearance of cachexia. Temperature 38.2–38.3°C. Pulse 108, regular, thready, and weak. Both apices had a dull sound. Many medium râles were heard at the right apex, over the frontal surface of the left lung and left interscapular region. Respiration sounds weak. The lower margin of the lungs showed no respiratory movement. No change was visible in the heart or the organs in the abdominal cavity. Von Pirquet reaction negative. 0.3 gm. of pyramidone was administered, and the

patient ordered to keep quiet. The temperature became normal in a week, when 6 cc. of cyanocuprol were given. No reaction developed, and the patient was allowed to go home. On the 6th day she ate some indigestible food and diarrhea occurred. Temperature 38°C. Pain in the bowels. On the following day she passed ten pus-like, mucous, bloody stools. No bacilli of tuberculosis or dysentery were found on bacteriological examination. The symptoms subsided in a week, the temperature falling gradually to 37.4°C. In the 2nd week after the first injection she was again admitted to the hospital and 5 cc. of cyanocuprol were given. The temperature, which remained at 37.8°C. before the injection, fell to 37.4°C. on the 4th day after the injection, perhaps in consequence of keeping quiet. After the third injection a severe angina developed and the temperature rose above 39°C. Appetite poor. A fourth injection of 4 cc. was given, and on the 7th day severe cerebral symptoms developed. Patellar reflex normal. Neck not stiff. Kernig's sign absent. The patient died on the 12th day after the fourth injection.

The intensification of the symptoms is not wholly due to the effect of cyanocuprol, but I have reported these three cases in order to show that failures may be encountered. The reactions sometimes appear after a week's delay. In case of such an abnormal reaction, special precautions should be taken. The severe cases and cases suffering from progressive lesions or with a poor prognosis seem especially to suffer from retarded reactions.

Care of the Patient.—Cyanocuprol brings about an improvement in the condition when adequate doses are administered; but this alone is not sufficient, for the condition may be intensified unless special care is taken. Besides the dose of the preparation, which must be regulated for each patient under treatment, care following the injection is essential. By care is meant rest. Disappointments in the past have been explained by the fact that this care had been neglected. Rest would seem to be easy to accomplish, but it is, in practice, one of the most difficult and complex conditions to meet.

It is a well known fact that the psychical condition of the patient influences disease. This is especially true in tuberculosis, for the disease itself is apt to increase the psychic sensibility.

Case 5.—Male; age 36 years. Large build. Family history negative. Pulmonary tuberculosis in the third stage, with intestinal (?) tuberculosis. Contracted pleurisy 8 years ago. Suffered from tuberculosis of the left lung 5 years ago, which gradually spread. In 1914 his case was diagnosed at the hospital

of the Tokyo Imperial University as probable intestinal tuberculosis. Nutrition poor. Slightly anemic. Pulse more than 85, regular. Temperature 38°C. Chest poorly developed. Respiration impaired. Dull sound over the left lung, except the lower lateral part where the sound is nearly normal. Many large and small râles are heard over this region and over the right apex and the right side. Wintrich's phenomenon present at the left subclavicular region. A hardening the size of a pigeon's egg, and slightly tender, is felt at the right iliac region. The first three injections of 5 cc. each were made every other week. The râles decreased and the intestines became less hard. The patient thought he had improved somewhat. 5.75 cc. were given at the fourth injection. On the day before the injection, he received news of the death of his elder sister. In consequence of this, severe emaciation developed and he became utterly helpless. A fifth injection of 5 cc. and a sixth of 4 cc. had no effect, and the administration of cyanocuprol was abandoned.

Case 6.—Female; age 22 years. Small build. Family history negative. Progressive form of pulmonary tuberculosis in the third stage. In her 15th year she was operated on for cervical lymphangitis. Has had no other serious disease. In Feb., 1915, she caught cold and has since suffered from coughing and expectoration. Since April she has been conscious of fever, with sudden increase of coughing and expectoration. Nutrition impaired. Moderately severe anemia. Subcutaneous fat diminished. Skin loose. Pulse more than 114, small, regular, thready, and weak. Cervical glands not palpable. Chest long and narrow. Respiration normal. From both apices to the first intercostal space as well as on both sides of the chest to the fifth rib a dull sound is heard. Throughout the lungs râles are heard, mingled with consonant râles. The lower margin of the lungs has weak respiratory movements. No change is noticed in the heart and various organs in the abdomen. Temperature 38–39°C. Body weight 34.7 kilos. 5 cc. were given for the first injection. No reaction was produced. 5 cc. were given for the second injection, which again produced no reaction. By this time decrease of rales was observed and the temperature became lower. The patient felt better. 4.5 cc. were given for the third injection, after which she ejected bloody sputum. Some members of her family told her about her hopeless condition which distressed her greatly. She was not able to sit up in bed, although by the 5th day after the injection the sputum was no longer bloody. Two more injections were made, but emaciation developed rapidly and she died soon after.

That untoward psychical influences act unfavorably upon tuberculosis has been shown in many cases. Patients who suffer from hypersusceptibility are difficult to treat, and special care must be used in the administration of cyanocuprol.

Rest for the Body.—During the reaction period, the body must be kept absolutely quiet, and the patient must not be allowed to move

about, or severe pneumonia may sometimes develop, as in Case 2. External excitement causes severe reactions which interfere with improvement. Hence while under treatment the patient must be kept under the special care of the physician in the hospital. In the Kitasato Institute the patients are ordered to rest as completely as in relapse in enteric fever. The period of rest varies according to the severity of the disease and other conditions of the patient. For example, the requirement is 3 days for a patient having pulmonary tuberculosis in the first stage, 5 days for the second stage, and 7 days for the third stage. If, however, the patient is suffering from fever, hemorrhage, progressive lesion, retarded reaction, pleurisy, peritonitis, and especially from kidney tuberculosis, the period is considerably prolonged. Even after the expiration of the set period of rest, it is better to keep quiet for another period in order to avoid all danger of fever. Fever or hemorrhage may develop in consequence of a trip by railroad as well as from exercise. The greatest care is demanded at the first and the second injections and no exercise permitted.

Rest for the Lesion.—Rest for the lesion alone produces improvement and, therefore, the splint or plaster bandage is extensively applied for bone or joint tuberculosis. Artificial pneumothorax may also accomplish a similar purpose. Rest for the lesion is an essential element in bringing about complete action of the remedy, and is no less important than rest for the body. The manner of giving rest to the lesion must differ with the form of the disease. The following methods may be indicated.

Pulmonary Tuberculosis.—Coughing and speaking must be stopped. Above all, the cough must be carefully treated, for an increase of the cough often involves danger. Coughing may be satisfactorily controlled by codeine hydrochloride or similar sedatives. To remove the difficulty of expectoration in consequence of tenacity of the sputum, or in nervous coughs, the bronchitis kettle will prove valuable. I usually treat these cases with a solution containing 1 gm. of sodium bicarbonate, 1 gm. of sodium chloride, and 100 cc. of distilled water, by means of a nasal atomizer used by the patient when the coughing returns. Dust must be excluded from the air breathed. Smoking and loud or long speaking must also be prohibited.

Pleurisy.—Breathing is comparatively less harmful in pulmonary tuberculosis, but in pleurisy the movements of the chest rub the lesion. This may cause the greater reaction and less efficacy of the preparation in pleurisy than in pulmonary tuberculosis. In pleurisy, therefore, the patient must not only follow all the necessary precautions required for pulmonary tuberculosis, but the period of rest for the body must be considerably prolonged.

Laryngeal Tuberculosis.—Speaking must be forbidden in cases in which hoarseness exists. Coughing also is more harmful in this condition than in pulmonary cases. Irritating food and smoking must be abstained from.

Intestinal and Peritoneal Tuberculosis.—The peristaltic contractions of the intestine necessarily interfere with the rest for the lesion in intestinal tuberculosis. At first severe reactions were obtained in tuberculosis of the bowels, but these inconveniences have now been eliminated. The precautions taken are briefly as follows: On the day before the injection a laxative such as magnesium sulphate is administered, and on the morning of the injection an enema of saline solution is given in order to evacuate the contents of the bowels. A comparatively less amount of cyanocuprol is then injected. If the patient does not have a stool the next day, an enema or some other treatment should be given in order to insure a daily stool. After the injection no food is to be taken that may produce diarrhea or increase fermentation, and stimulating food accessories or indigestible foods are omitted. Morphine or its derivatives may be resorted to in order to control peristalsis, but they usually cause constipation and consequently incur fermentation, thus leading to stimulation of the intestinal lesions. When a severe enteric reaction arises producing symptoms resembling acute dysentery, morphine may be administered.

Surgical Tuberculosis.—For cutaneous or glandular tuberculosis, no special precaution is necessarily taken except that the lesion should not be exposed to outward stimulation. For bone or joint tuberculosis, a splint or plaster bandage should be applied.

Kidney Tuberculosis.—Similar precautions to those taken in acute nephritis are recommended. For example, stimulating foodstuffs should be strictly prohibited and the patient should be ordered to

take absolute rest. Thus far only a few cases of kidney tuberculosis have been treated.

It is an interesting fact that an intimate correlation between the doses and the rest for the lesion seems to exist. The doses given above have been established by experience. For example, small doses are prescribed in pleurisy, intestinal tuberculosis, and laryngeal tuberculosis; while in surgical cases larger doses are given. The results of the treatment also seem better in the latter than in the former conditions. The difference may possibly be accounted for by the fact that in the former cases, the drug produces severe lesional stimulation which interferes with the improvement. The only practical way of eliminating these unfavorable influences and of establishing improvement is by securing rest for the lesion.

Contraindications.—Koga points out that apricot juice must not be given with cyanocuprol, because of the increase of hydrocyanic acid, while potassium iodide, creosote, guaiacol, and their derivatives, serve to produce severe reactions, and hence all are contraindicated. It is well known that potassium iodide exerts an influence upon tuberculous lesions, for it causes inflammation at the site of the lesion. The precise action of creosote and guaiacol is not yet determined, but it is known that their hypodermic or intravenous administration produces sudden increase of the lesional reaction. All remedies which produce lesional inflammatory effects must be avoided.

Can tuberculin be given coincidentally with cyanocuprol? Koga reports that in a patient that had been treated with tuberculin, cyanocuprol produced a remarkable improvement, while the reactions had been slighter than in patients who had not had tuberculin. But it is better to avoid tuberculin while cyanocuprol is being administered, for the lesion will become sensitive to the various influences. The precise doses of tuberculin and cyanocuprol are not easily established and the combined treatment is not advised. If, however, cyanocuprol should be ineffective, tuberculin may be resorted to after a considerable interval.

The following case is of interest, as it had previously been treated with iodol.

Case 7.—Male; age 49 years. Large build. Mother and wife died of pulmonary tuberculosis. Pleurisy on both sides. Both apices infiltrated. He

has always been healthy and has never had any serious illness. Has been suffering from pleurisy since last year. Temperature had been about 39°C. at first. At present it is nearly normal. Heart frequency increased, and weakness set in. Appetite and nutrition impaired. Constipated. Color pale. Pulse more than 80, regular, medium tension. Dull sound from the apex of the right lung to the first rib in front, and the same region on the back, and at the side of the apex of the left lung. The lower lobes of both lungs have also a dull sound on the back and front. Breath sounds weak throughout. Voice vibrating and weak. On the frontal side of the lungs râles are heard. In the upper lobes on both sides of both lungs bronchial sounds are heard. 5 cc. of cyanocuprol were given at the first injection. Temperature rose to 37.7°C. The next evening it rose to 38.4°C. On the 3rd day it rose to 39.1°C. No unfavorable symptoms were observed in the chest, but the patient complained of pain in the muscles of both hips. Two hard swellings the size of hen's eggs were observed on the left side and one on the right. They were tender and felt like gristle. The patient states that they correspond to the injection points of iodol, which was given 2 months ago, and that they showed no change before cyanocuprol was given. On the 7th day the temperature fell below 37°C., but rose again to 38°C. A second injection of 4 cc. was made 3 weeks after the first. No reaction was produced and the temperature remained below 37.1°C. A third injection of 4 cc. was given 2 weeks after the second. It produced no reaction. The swellings on the hip became smaller,—no larger than a nut. They remained unchanged by the injection of cyanocuprol, and the tenderness disappeared. Symptoms of pleurisy gradually improved. The rise of temperature after the first injection seems to indicate that an intimate relation exists between the two substances.

All the agents used in symptomatic treatment, such as pyramidone, aspirin, codeine, morphine, bismuth chloride, tannigen and its derivatives, ergotine and its derivatives, digitalis and its derivatives, digestive adjuvants, etc., may be given with cyanocuprol. A general diet may also be given except in the cases mentioned.

Prognosis.—The fundamental criteria on which prognosis is based are the same with the cyanocuprol treatment as with other agents. Patients with a noteworthy family history or those in whom there is no von Pirquet reaction except when treated with tuberculin have, as a rule, a bad prognosis. The older lesions apparently are slow to react to the drug. Age seems also to interfere with its action. An acute progressive form of the disease must be treated with special precautions. Even when applied with the utmost care patients suffering from acute lesions have sometimes seemed not to do well under the treatment.

Case 8.—Male; age 37 years. Large build. Family history negative. Progressive form of pulmonary tuberculosis in the first stage. Has always been healthy; no serious illness. Contracted bronchitis in Oct., 1914, from which he recovered in Feb., 1915. In the same month he complained of recurrent bronchitis. Since then he has had moderate coughing and expectoration and sometimes night sweats. Appetite good. One or two stools a day. Nutrition poor. Anemic. Face pale. Two or three swellings as large as peas are present in the cervical glands. The laryngeal mucous membrane is pale. Pulse more than 100, small, regular. Chest long and narrow. Breathing good. Percussion normal. On deep inspiration a few medium râles are heard in the left lung. Respiration sound generally weak. Heart and abdominal organs normal. Von Pirquet reaction slightly positive. The bacilli in the sputum are equal to Gaffky's No. I. The first injection of 7.75 cc. was made when the body temperature was 38°C. It rose to 39°C. the same afternoon. It became normal in 3 or 4 days, and the râles decreased. In 2 weeks crepitations were heard at the third rib in front and in the left scapular region. A second injection of the same dose was given. This time no fever was produced. In 2 weeks, however, the crepitations in the right side of the chest changed to consonant râles. Those on the right side developed moderate consonant râles. A moderate number of râles appeared on both sides. The same dose was given at the third injection. No reaction appeared immediately, but in a week the temperature began to rise and reached 39°C. in 12 days. Râles also increased. At the right apex a dull sound was heard. In 18 days the temperature fell to 38°C. On the 25th day after the last injection the patient received a fourth injection of 6.5 cc. No rise of temperature was observed, but the râles increased. In 2 weeks a fifth injection of 5 cc. was given, and the temperature began to rise. On the 4th day it was 39.4°C. In 2 weeks a sixth injection of 4 cc. was given The temperature fell this time in a week to 38.3°C., and again rose to 39.5°C. Edema developed on the face and dorsal part of the feet. A slight anesthesia developed at the lips, abdomen, and legs, with slight tenderness in the calves. Heart normal. He probably suffered from beri-beri. A seventh injection of 3.5 cc. was given. No reaction occurred. The symptoms of beri-beri disappeared after 2 weeks of a rice-free diet and treatment with cascara and magnesium sulphate. An eighth injection of 3 cc., a ninth of 2.5 cc., and a tenth of 2.5 cc. were given. Each time no reaction occurred. The râles decreased markedly after the sixth injection. A slight dull sound appeared at the left apex after the seventh injection. Great weakness developed. The patient is still under treatment.

Idiosyncrasy and Accumulative Effect.—A severe case is generally highly susceptible to cyanocuprol. Patients in whom it is difficult to keep the lesion quiet or nervous patients sometimes suffer from severe reactions. There are still others in whom no cause for the

reaction can be accounted for. I have not yet enough data to decide whether they comprise an idiosyncrasy or not.

After the injection of cyanocuprol the lesion becomes susceptible to irritation, but on repetition of the injection no increase in the irritation has been noted. In other words, no case has been met with in which an accumulative effect of cyanocuprol was observed.

Cases in Which Cyanocuprol Did Not Lead to Improvement.

Case 9.—Male; age 33 years. Average build. Family history negative. Infiltration of the left upper lobe; tuberculosis of the right upper and lower lobes. Has always been healthy except for pleurisy in his 16th year and epidemic cerebrospinal meningitis in his 28th year. Coughing for about 1 year. Night sweats. Conscious of fever. Nutrition fair. Face pale. Pulse regular, tension normal. Chest long and narrow. Respiration good. Dull sound present from the apex of the left lung to the second intercostal space in front and the middle of the scapula. Moderate non-consonant râles from the apex of the left lung to the middle of the scapula and over the surface of the left lung in front. The same kind of râles heard over the region corresponding to the upper lobe of the right lung. Maximum temperature 37.2°C. Body weight 49.9 kilos. 7.5 cc. were given at the first injection. 2 weeks later 7.75 cc. were injected. After the second injection many tubercle bacilli were present in the sputum. Sputum has been ejected the same number of times daily as before; *i.e.*, two or three times. Since then 7 to 8 cc. of cyanocuprol have been injected every other week, but no ill effects have been observed. The only change in the symptoms has been a slight decrease of the dull sound in the upper lobe of the left lung, while a slight dull sound has developed at the apex of the left lung and the râles in the left lung have decreased slightly. Tubercle bacilli in the sputum range between 0 to No. VIII of Gaffky's table. A slight rise of temperature was observed after the seventh injection, 37.5°C., rarely 38°C. In this case cyanocuprol had no effect. Body weight lost 3.8 kilos. The patient says he has lost in body weight every summer.

Case 10.—Male; age 33 years. Average build. Had seven brothers and sisters, two of whom died of pulmonary tuberculosis. Pulmonary tuberculosis in the first stage. Has never been strong, but has had no serious illness. In July, 1914, he had hemoptysis. In Jan. and Feb., 1915, the sputum was again bloody. Temperature normal. Sleep interrupted. Appeared generally nervous. Cough and expectoration moderate. Appetite impaired. Nutrition fair. Face pale. Pulse regular, more than 85. Chest moderately developed. Respiration good. No swelling present in the cervical glands. No abnormal dull sound is heard in the chest. A few small râles are heard at the lower margins of both lungs. No abnormal symptoms are present in the heart and the organs

in the abdominal cavity. Von Pirquet reaction weakly positive. Tubercle bacilli in the sputum correspond to Gaffky's No. VIII. 7.5 cc. of cyanocuprol were given at the first injection. A slight increase in the râles was observed the next day, which decreased on the 3rd day. In 2 weeks they could be heard only when he coughed. 7.5 cc. of cyanocuprol were given at the second injection. No reaction. 7.5 cc. were given at the third injection. A slight decrease was observed in the râles which were heard at the time of coughing. No reaction present. For the fourth, fifth, and sixth injections 7.5, 7.25, and 7 cc. were given, respectively. No reactions produced. The bacilli in the sputum decreased to Gaffky's No. II to No. IV. They could not be eliminated. The râles also never subsided. Sleep was interrupted as before. The body weight decreased 2.6 kilos.

Case 11.—Male; age 22 years. Tall and thin. Mother died of pulmonary tuberculosis accompanied by intestinal tuberculosis, and one younger brother died of pulmonary tuberculosis. Pulmonary tuberculosis in the second stage, and intestinal tuberculosis. Has had no serious illness, but is subject to gastro-intestinal disturbances. For 20 days has felt feverish and had night sweats. Coughing and expectoration slight. Appetite impaired. Great emaciation. Face and mucous membrane of the mouth and the eyelids highly anemic. Chest long and narrow. Respiration good. The upper lobes of the right and left lungs have medium râles. Crepitation is heard at the lower part of the right lung. Abdomen is a little sunken. A hard mass as large as a pigeon's egg is felt at the cecum. The region around the navel is tender to the touch. Temperature 37.3°C. Pulse over 90. Body weight 41.8 kilos. The first, second, and third injections consisted of 7, 7, and 6.75 cc., respectively. After the third injection the râles in the left apex increased. The fourth, fifth, sixth, and seventh injections consisted of 7, 7, 6, and 6 cc., respectively. After the fifth injection the temperature rose to 37.5°C., but after that no rise was observed. Once after bathing it rose to 38°C., and at another time after he had eaten ice-cream when he was out of the hospital, it rose to 38.6°C. On another occasion he ate ice-cream while in bed in the hospital and the temperature rose as high as 38°C. For 9 days after the 4th day after the third injection, it ranged between 37.4–38.3°C. At the time of the seventh injection all the râles disappeared except those in the right apex. The hard mass as well as the tenderness around the cecum also disappeared. Dullness remained the same. Diarrhea remained the same as before the treatment; two or three stools daily. Emaciation developed gradually. Body weight lost 6.5 kilos. Bacilli had not been observed in the sputum at the beginning of the treatment but they became visible after the fourth injection and never disappeared. After the seventh injection he was subjected to dietetic treatment and cyanocuprol was suspended, but in spite of the effort to gain in strength, there was no improvement. The temperature remained about 38°C.

Cases in Which Cyanocuprol Produced Some Improvement.

Case 12.—Female; age 23 years. Family history negative. Infiltration of the apex of the left lung. Has been healthy. In 19th year contracted inflammation of the internal ear. 2 years ago she says she contracted pleurisy and intestinal tuberculosis. In Oct., 1914, she contracted tuberculosis of the apex of the right lung. Moderate coughing and expectoration. Occasional night sweats. Temperature 37.3°C. Nutrition fair. Color good. Pulse regular and normal. No swellings present in the cervical glands. Heart and organs in the abdominal cavity normal. Both tonsils enlarged. Mucous membrane of the larynx flushed. Spine curved to the left. Chest medium. Respiration good. A slight dull sound and a few small râles are heard throughout the left lung. Respiration weak at the lower margin of the left lung. The bacilli in the sputum are equal to Gaffky's No. III. Body weight 50.5 kilos. Von Pirquet test strongly positive. 7.5 cc. of cyanocuprol were given at the first injection. The temperature rose to 37.6°C. Coughing increased considerably. The temperature remained at 37.5°C. The same dose was given for the second, third, and fourth injections. No reaction was produced. The temperature fell to 37.3°C. after the second injection. 7.75 cc. were given for the fifth injection. This time slight fever was produced, for it remained at 37.7°C. for about a week, after which it again fell below 37°C. All the symptoms in the lungs decreased markedly after the first injection. Nearly all the dull sound as well as the râles disappeared. Expectoration disappeared after the first injection. No sputum could be obtained for bacteriological examination. Occasional inflammation of the tonsils, but no other complaints. Body weight lost 0.9 kilo.

Case 13.—Male; age 29 years. Average build. Father died of an intestinal disease. Two brothers died of meningitis. One maternal uncle died of tuberculosis. Infiltration of the upper lobes of both lungs. Patient has always been healthy except for pleurisy in his 18th year. Had pulmonary hemorrhage 4 years ago and another attack 4 months ago. At present he coughs and expectorates a little. Color good. No swelling occurs in the cervical glands. Pulse, heart, and organs in the abdominal cavity normal. Temperature normal. Chest poorly developed. Respiration weak. A slight dull sound is heard over the region from the apex down to the first rib in front and the middle of the scapula on the back. Medium râles are heard along the left lung. At the lower part of the left lung a slight dull sound is heard. The bacilli in the sputum correspond to Gaffky's No. III. Body weight 51 kilos. Von Pirquet test weakly positive. 7.75 cc. of cyanocuprol were given for the first, second, and third injections. 7.75 cc. were given for the fourth and the fifth injections, respectively. A slight increase in the râles was observed after the first, third, and fifth injections, and decrease of the dull sound was noticed. The latter remained to a slight degree on the back of both lungs and the apex of the right lung. The râles also nearly disappeared, remaining only on the back of the right lung.

The bacilli in the sputum became so few that in the ordinary film preparation none could be detected. Body weight gained 0.5 kilo.

Case 14.—Male; age 25 years. Father died of tuberculosis. Pulmonary tuberculosis in the third stage. Caries of the fifth rib and tuberculosis of the cervical glands. Has been healthy. In 7th year contracted diphtheria. In 21st year contracted tuberculosis of the cervical glands, and consequently developed anesthesia of both ears. 3 years ago remittent fever developed, ranging between 37 and 39°C. At the same time coughing and expectoration appeared. In April of last year had three hemoptyses, each time losing about 100 cc. of blood. Emaciation. At present the temperature is 37.5–38°C. Occasional hemoptyses. Moderate coughing and expectoration. Emaciation becoming more severe. Von Pirquet test negative. Nutrition poor. Face pale. Lips flushed. Swellings as large as the tip of the little finger present in the cervical glands on both sides. Scars at the left side of the neck and over the fifth costal cartilage on the right are both due to an operation. Closed pustulation as large as a pigeon's egg present at the lower frontal part of the sternum. Pulse more than 90, regular, tension slightly decreased. Chest narrow, especially on the left side. Dull sound over the surface of the left lung. From the apex to the second intercostal space on the right frontal side and the lower end of the scapula on the back is heard a slightly dull sound. Over the whole region where the dull sound prevails and at the region corresponding to the lower lobe of the right lung consonant large and medium râles are heard. Dimension of heart could not be determined. Heart sound normal. Abdomen normal. Body weight 45 kilos. 6.5 cc. were given at the first injection. The following injections were made every other week, each dose being 5 cc. No ill effects appeared. After the fourth injection the temperature did not rise above 37.4°C. The general condition of the patient improved greatly. The dull sound as well as the râles became considerably less. The bacilli in the sputum, which corresponded to Gaffky's No. VIII, never exceeded Gaffky's 0 to No. III. The body weight gained 0.3 kilo.

Case 15.—Female; age 17 years. Average build. An elder sister died of pulmonary tuberculosis. Pulmonary tuberculosis in the third stage, acute, progressive form. Has always been healthy. A year ago suffered from coughing and expectoration, the temperature reaching sometimes as high as 38–39°C., which always subsided in several days. A similar attack occurred 9 months ago and was diagnosed as pleurisy. Severe coughing and night sweats occurred. Nutrition fair. Face pale. Lips cyanotic. Mucous membrane of the eyelids and mouth pale. No swelling present in the cervical glands. Pulse small, regular, and over 90. Chest long and narrow. Respiration weak. The heart beat is conspicuous at the second and third intercostal space. Dull sounds are heard over the surface of the right frontal side of the lung to the second intercostal space on the left and to the lower edge of the right scapula, and over nearly all the surface of the right lung on the back. Many large and medium râles are heard over the whole sur-

face of both lungs except the lower dorsal part. The heart is normal except for a slight hemic murmur. Abdominal organs all normal. Temperature is 38–39°C. Body weight 37.5 kilos. 6.5 cc. of cyanocuprol were given at the first injection. It produced a local reaction. A second injection of 6 cc. and a third of 6.25 cc. were given. 2 or 3 hours after the third injection the temperature rose to 38.4°C., which soon subsided and remained below 37°C. All the symptoms improved considerably. At the fourth, fifth, sixth, and seventh injections, the doses were 6.25 cc. After the fourth injection the temperature did not rise above 37.4°C. Night sweats practically subsided. Severe pathological processes completely checked. At the eighth and ninth injections 6.5 cc. were given. The dull sound and the râles had become considerably less. After the ninth injection the temperature rose to 37.7°C. and resulted in a slight increase of the dull sound and râles. For the tenth injection 5 cc. were given. The patient is still being treated.

Case 16.—Male; age 20 years. Family history negative. Infiltration of the upper lobe of the right lung and peritoneal tuberculosis. In 13th year contracted pleurisy. In 17th year had a little bloody sputum. For 4 months has been complaining of general dullness. Some months ago swelling of the abdomen and pain in the region of the stomach developed. He has been conscious of fever several times a day. No coughing or expectoration. Appetite normal. Stools once every other day; occasional diarrhea. Respiration labored and deep. Nutrition good. Not anemic. Pulse regular and normal. Chest well developed. Slight dull sound is heard at the upper lobe of the right lung. At the right lateral upper part is heard a clear bronchial respiration sound. Many medium râles at the right apex. The right axillary cavity has a dull sound and a few crepitations. Respiration normal at the lower edges of the lungs. Abdomen swollen; right side resistant. In the right iliac cavity is a tender hard mass as large as a pigeon's egg. No exudate is present in the abdominal cavity. Temperature 37.3°C. Body weight 60.1 kilos. 7.75 cc. of cyanocuprol were given at the first injection. On the following day suffered from dizziness; temperature rose to 39.4°C. It fell to the usual point the next day. This is one of the highest febrile reactions that I observed, the temperature varying 2.1°C. A second injection of 7.75 cc., a third of 7.75 cc., and a fourth of 7.5 cc. were given; no reaction followed. After the first injection, the resistance of the abdomen disappeared rapidly. The dull sound of the lung also disappeared, and the râles became fewer. At the fourth injection the symptoms of the lungs and the resistance of the abdominal wall had disappeared completely. The patient did not follow the prescribed diet, and the hard mass in the right iliac cavity became more prominent. He suffered from diarrhea. Body weight lost 1.2 kilos.

Case 17.—Female; age 33 years. Husband suffering from a light case of pulmonary tuberculosis. Caries of the sixth dorsal and the fourth lumbar vertebræ. Infiltration of the apex of the right lung. Patient has always been healthy; no noteworthy illness. 9 months ago she began to complain of general dullness

and occasional fever. No coughing or expectoration. Occasional pain in the left side of the chest. Pain in the back and hips when moving. Appetite normal. No night sweats. Nutrition fair. Slightly anemic. Pulse regular, tension good, more than 78. Right submaxillary glands slightly enlarged. Chest long and narrow. Respiration normal. A slightly dull sound is heard at the apex of the right lung. Crepitations are heard at the second and third intercostal spaces on the left side. The sixth dorsal and the fourth lumbar vertebral processes are tender. Heart and abdominal organs normal. Reflex of knee joint normal. 7.5 cc. of cyanocuprol were given at the first injection. Crepitation increased. The second, third, fourth, and fifth injections were given, the doses being the same as the first. A sixth injection of 7 cc. was given. No reaction developed. The symptoms of the lungs disappeared almost completely, except for a slight weakness of the respiratory sound. A year ago she began to suffer from hiccough, which occurred for 2 or 3 hours daily. This ceased entirely after the third injection. At the same time the pain in the chest disappeared, and there are no other symptoms. She conceived 1 month before the first injection was given. Cyanocuprol had no influence upon pregnancy in this case.

Case 18.—Female; age 28 years. Family history negative. Pulmonary tuberculosis in the second stage and intestinal tuberculosis. Pregnant 7 months. Has always been healthy. A month ago she began to suffer from coughs, fever, pain in the stomach, etc. Diarrhea six or seven times daily. No expectoration. Nutrition poor. Very anemic. Temperature 38°C. Pulse more than 90, regular, weak. Chest long and narrow. Respiration weak. No swelling in the cervical glands. The apices of the lungs and the lower side of the left lung have a slightly dull sound. A tympanic sound is heard at the side of the left apex. Numerous medium râles are heard over the side and front of the left lung. A bronchial respiration sound is heard at the upper frontal side of both lungs and the interscapular region. The abdominal region is swollen and the swollen uterus can be felt. Above the uterus is felt a movable soft mass lying longitudinally. It is slightly tender. In the right iliac cavity there is a tender region. Owing to pregnancy minute particulars could not be determined. Body weight is 42.2 kilos. 4 cc. of cyanocuprol were given at the first injection. After the injection the temperature rose as high as 38.7°C. On the following day it fell to the usual point. The patient complained of a slight pain in the abdomen. No change occurred in the symptoms of the lungs. From the 5th day after the first injection the temperature did not exceed 37.2°C. Diarrhea decreased to one or two times daily. Abdominal pain also subsided. 5 cc. were given for the second injection. No reaction occurrred. Diarrhea stopped. A third injection of 5 cc. and a fourth of 4.5 cc. were given. The temperature rose to 37.4°C., and fell to 37°C. on the 3rd day. The dull sound decreased a little but no change occurred in the râles. As labor approached the treatment was suspended. Cyanocuprol again produced no harmful effect on pregnancy. The intestinal tuberculosis improved greatly, but the pulmonary symptoms remained unimproved.

I deem it proper to state here that the cases which have improved and which ceased to receive further treatment have been examined afterwards from time to time, and thus far have rarely relapsed. Moreover, those that had some slight symptoms left when they ceased to receive cyanocuprol were found to have continued to improve without receiving further medical treatment. I have seen no case in which the symptoms increased after the completion of the treatment with cyanocuprol.

SUMMARY.

Cyanocuprol is markedly effective in tuberculosis, and we believe that it will play an important part in clinical medicine. It may be used more generally than tuberculin.

The amount of the dose is closely related to the reaction and the final results. It should be determined for each patient after a careful examination of his symptoms. The maximum dose of 8.5 cc. should in no case be exceeded.

The shortest interval between injections should be 2 weeks. If the drug is given after a shorter interval, no improvement is observed and the effects are sometimes dangerous.

In order to obtain the best results the patient should be placed under conditions of complete physical and mental rest after the injection; this applies even to light cases. Care should also be taken to secure rest for the lesion.

During the period of the treatment irritants to the lesion, such as potassium iodide or tuberculin, should be avoided; apricot juice, guaiacol and its derivatives, and iodol are contraindicated.

No marked idiosyncrasy has been noted and no accumulative effects have been observed.

I desire to express my indebtedness to Dr. Kitasato for privileges in connection with the execution of the present work and to Dr. Koga and Mr. Nemoto for suggestions and assistance.

THE TREATMENT OF LEPROSY WITH CYANOCUPROL.

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(Received for publication, December 1, 1915.)

The present communication is a brief report upon the use of cyanocuprol in the treatment of leprosy. Cyanocuprol has proven of value in the treatment of tuberculosis in animals and has been employed also in the treatment of human cases of the disease.[1] Hence it was concluded to test its chemotherapeutic action in leprosy. Thus far no specific treatment for leprosy has been discovered, and I am presenting this report, though brief, for it seems to contain an advance at least in the treatment of that malady.

Because of a similarity which exists between the bacilli of leprosy and tuberculosis, the attempt to apply the same curative substances both to tuberculosis and to leprosy seems reasonable. Since the experimental production of leprosy in animals has not been effected and since cultivation of the bacillus of leprosy has not yet been surely accomplished, the application of proposed curative substances must necessarily be made to human cases directly. In this instance the chemical preparation has been administered to numerous human patients on a basis of established clinical observation.

In the treatment of tuberculosis with cyanocuprol special attention was paid to the local and general reaction, because in tuberculosis an intimate relation seems to exist between the dose and the pathological process. It was anticipated that the local reaction would be of consequence in the treatment of leprosy, for the local lesions chiefly occupy the surface of the body; but contrary to my idea no such reactions occurred. Moreover, general reactions were also absent.

At first 16 to 20 mg. were given every other week. I have now come to the conclusion that 20 to 24 mg. may be given weekly without ill effects. The administration was exclusively by intravenous

[1] Koga, G., *J. Exp. Med.*, 1916, xxiv, 107, 149.

injection with an ordinary syringe, the needle being inserted into the femoral vein. The injection is made very slowly. After seven or eight injections symptoms such as congestion of the head, forcible deep breathing, acceleration of the pulse, etc., similar to what is known as anaphylactoid in salvarsan injections have been encountered. But the symptoms are fleeting, and recovery occurs in a moment without discomfort. Women are more often affected than men. These effects can, however, be obviated if the injection is made slowly enough and the patient is allowed to rest for a short time after the operation.

The following are the reports of cases of leprosy treated in the I-hai-yen Leprosorium, Meguro Village in Tokyo. More detailed reports will be made later.

Case 1.—T. H., female, aged 25 years. Lepra maculosa. No family history. In February 1914, local anesthesia and pigmentation appeared on the right arm. Confined in December of the same year. At that time a great many large and small spots appeared all over the surface of the body. I examined the patient first in April, 1915. Her face was dark purple in color with many infiltrations in the skin. Many spots as large as the tip of the little finger were scattered over the face, arms, and body, which lacked sensation. An injection of 10 mg. was given on Apr. 22. No rise of temperature occurred, or any other ill effects. A second injection of 10 mg. was given on May 10. After the injection the lesions presented slight congestion. A peculiar sensation was felt in the arms. A third injection of 8 mg. was given on May 24, after which the general symptoms seemed to improve. A fourth injection of 8 mg., a fifth of 8 mg., a sixth of 10 mg., a seventh of 12 mg., and an eighth of 12 mg. were given successively on May 28 and June 3, 10, 17, and 28. During this period the infiltration and the pigmentation of the face gradually disappeared and the skin recovered a healthy color. A ninth injection of 12 mg. was given on July 5. This time, immediately after the injection, the patient complained of congestion in her head. A still stronger congestion was experienced after the tenth injection of 12 mg. on July 12. In each instance the congestion subsided in a few minutes. An eleventh injection of 10 mg., a twelfth of 10 mg., a thirteenth of 10 mg., a fourteenth of 10 mg., and a fifteenth of 10 mg. were given successively on July 20 and 26, and Aug. 2, 9, and 16. Each time a fleeting sensation of congestion occurred.

Gradual improvement of the symptoms has been observed since the first injection. The color of the face and the consistency of the skin have become nearly normal. Sensation has also been almost completely restored. However, several anesthetic, roseola-like spots still remain in the submaxillary region. The spots on the other parts of the body have become white, and sensation has

been completely restored. Some of the spots have assumed a normal color. Nutrition good.

Case 2.—H. O., female, aged 23 years. Lepra maculosa and anæsthetica. No family history. The first symptoms appeared 3 years ago. They seemed to improve for a while but became worse during the spring of 1915. I examined the patient for the first time in May, when most of her face was covered with dark red spots. The same kind of spots was present on both arms. The left little finger became withered and could hardly be clenched. Infiltration occurred in the spot. Sensation lacking. The first injection of 10 mg. was given on May 20. No reaction occurred. The second injection of 8 mg. was given on May 29. The infiltration of the skin seemed to improve greatly. A third injection of 8 mg., a fourth of 10 mg., a fifth of 12 mg., a sixth of 12 mg., and a seventh of 12 mg. were given successively on June 3, 10, 17, and 28, and July 2. Immediately after the seventh injection the patient suffered from a fleeting congestive feeling in her head. An eighth injection of 12 mg. was given on July 12, when there was still stronger congestion. A ninth of 10 mg., a tenth of 9 mg., an eleventh of 10 mg., a twelfth of 10 mg., and a thirteenth of 11 mg. were given successively on July 20 and 26, and Aug. 2, 9, and 16. All the last five injections were accompanied by congestion in the head.

A fourteenth injection of 11 mg. and a fifteenth of 11 mg. were given on Aug. 23 and 26, respectively. In the last two injections the liquid was introduced very slowly into the vein, and no reaction occurred.

At present the facial spots are hardly noticeable. All the other spots are becoming paler, and sensation is gradually being restored. The left little finger is gradually recovering its motility, but is still withered; the tips of the fingers are becoming rounder in form and the palm is becoming thicker. Nutrition good.

Case 3.—J. Y., male, aged 17 years. Lepra maculosa and anæsthetica. One of his brothers is a leper. The symptoms appeared first in 1914. I examined the patient for the first time in May, 1915. His right hand is withered and the fingers cannot be clenched or opened. On the inner side of the joint of the right arm, a spot accompanying thickening of the skin occurred. On the inner side of the lower right arm a row of small protuberant spots was present. On the exterior side of both upper legs were a great many spots.

The first injection of 10 mg. was given on May 10, and was accompanied by no reaction. A second injection of 10 mg. was given on May 20, and a third of 8 mg. on May 28. The symptoms in the right arm improved. A fourth injection of 18 mg., a fifth of 11 mg., a sixth of 12 mg., a seventh of 12 mg., an eighth of 12 mg., and a ninth of 12 mg. were given successively on June 3, 10, 17, and 28, and July 5 and 12. After the last injection congestion of the head was felt. A tenth injection of 10 mg. was given on July 20, which produced a slight feeling of congestion in the head. An eleventh injection of 10 mg., given on July 26, was accompanied by the same reaction. A twelfth injection of 10 mg. was given on Aug. 2. The patient was allowed to lie still during the operation and no reaction occurred after the injection. A thirteenth injection of 11 mg., a

fourteenth of 11 mg., a fifteenth of 11 mg., and a sixteenth of 11 mg. were given successively on Aug. 9, 16, 23, and 26.

The infiltration of the spots in the region of the joint of the right arm has disappeared, and the pigmentation and infiltration of the small nodular spots has improved. There appears little or no trace of leprous changes. One of the fingers which could not be moved recovered its motility somewhat, as well as its power of sensation. The spots on the back and legs are becoming whiter in color and gradually disappearing. Nutrition good.

Case 4.—R. O., male, aged 35 years. Lepra maculosa and anæsthetica. No family history. The symptoms first appeared several years ago; recently new spots began to appear on the upper and lower limbs. Neurasthenia occurred occasionally. The first injection of 6 mg. was given on May 28. No reaction followed. A second injection of 10 mg. was given on July 5, when the tone of the pigment was observed to fade. A third injection of 10 mg. and a fourth of 10 mg. were given on July 12 and 20, respectively. The spots became very indistinct. After the fifth injection of 10 mg., given on July 26, congestion was felt in the head. A sixth injection of 10 mg., given on Aug. 2, was made while the patient was allowed to lie quietly in bed and no feeling of congestion in the head insued. A seventh injection of 10 mg., an eighth of 10 mg., a ninth of 10 mg., a tenth of 11 mg., and an eleventh of 10 mg. were given successively on Aug. 9, 16, 19, 23, and 26.

Both the old and new spots are fading. No neurasthenia. Sensation is gradually being restored. The patient is receiving the injection twice a week, without any unfavorable reaction. Nutrition good.

Case 5.—N. K., male, aged 28 years. Complicated leprosy. No family history. At the review of the militia in 1915, he was found to have leprosy. A slight infiltration occurred all over the face. At the right arm joint three nodules as big as peas were present. Some small subcutaneous nodules were felt on both calves. The external side of the lower left limb was anesthetic.

A first injection of 10 mg., a second of 10 mg., a third of 10 mg., and a fourth of 10 mg. were given successively on Aug. 2, 9, 16, and 23.

After the first injection the nodules in the right arm were absorbed, leaving brownish spots. By the fourth injection, two of the three spots became white and sensation was restored. The remaining one is still anesthetic. The nodules on the calves are softer, while the face is paler. The anesthesia of the lower left leg is recovering. Nutrition good.

Case 6.—K. Y., male, aged 34 years. Complicated leprosy; has pulmonary tuberculosis. No family history. Small nodules occurred all over the face. Spots were also present at the left elbow and the right knee. On the exterior side of the lower right arm, a protuberant spot was present. There were some small nodules on the calves.

The first injection of 9 mg., given on Aug. 2, was accompanied by dyspnea. The temperature rose as high as 38.5°C. This reaction occurred invariably in tuberculosis. A second injection of 9 mg., a third of 10 mg., and a fourth

of 10 mg. were given successively on Aug. 9, 16, and 23. The last injection caused a rise of temperature of 37.5–37.6°C.

The infiltration of the face is fading. The nodules became more conspicuous for a while, but became gradually smaller. The infiltration in the spots of the left elbow is becoming softer. The nodules of the calves are also becoming softer. The tubercular lesions are becoming very small.

I have injected cyanocuprol three times in more than ten cases and twice in more than twenty cases with old lesions. Some of them showed great improvement. A more detailed report will be published later.

SUMMARY.

This brief report deals with six cases of leprosy in which cyanocuprol has been administered with what appear to be beneficial effects. The treatment is being continued in still other cases.